Chapter 8. Cardiovascular Health Effects

A summary of the conclusions regarding the evidence of a causal association between ETS exposure and cardiovascular effects from the 1997 OEHHA report and this update are provided below. Table 8.01 presents conclusions regarding the cardiovascular outcomes of coronary heart disease (CHD) and stroke. The conclusions in Table 8.02 relate to changes in the cardiovascular system that contribute to the outcomes in Table 8.01. These conclusions are based on a weight of evidence approach. In summary, there is evidence that exposure to ETS causes coronary heart disease, and pathophysiological changes. In addition, there is evidence suggestive of an association between ETS exposure and stroke, and exercise tolerance.

Table 8.01 ETS and Cardiovascular Outcomes: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Finding OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
CHD	18	11[a]	Conclusive	Conclusive
Stroke	0	3	Not assessed	Suggestive

[a]Includes eight epidemiological studies and three meta-analyses

Table 8.02 ETS and Acute Cardiovascular Effects: Comparison of OEHHA (1997) and Update

Outcome	# Studies 1997	#Additional Studies in Update	Finding OEHHA 1997 Evidence of causal association?	Findings Update Evidence of causal association?
Impaired vascular and platelet function[a]	6	9[b]	Suggestive	Conclusive
Exercise tolerance	4	0	Suggestive	Suggestive

[a]Including aortic distensibility and reactivity, intima-media thickness, lesion formation, platelet aggregation, and altered blood lipids. [b]Includes seven epidemiological and two animal studies

8.0. Introduction

The association between coronary heart disease (CHD) and exposure to environmental tobacco smoke (ETS) was examined in OEHHA's 1997 report (Cal EPA, 1997). The following is from the conclusion presented in that report:

> "In summary, the epidemiological data, from prospective and case-control studies conducted in diverse populations, in males and in females, in western and eastern countries, are supportive of a causal association between ETS exposure from spouses and CHD mortality in nonsmokers."

This chapter reviews the relationship between cardiovascular disease and ETS exposure in light of the epidemiological studies, meta-analyses and related research published since the 1997 report. Various contributing conditions and endpoints of cardiovascular disease were measured in the studies reviewed below, including myocardial infarction (MI), ischemic stroke, coronary flow velocity reserve (CFVR), flow-mediated dilatation (FMD), aortic responsiveness and elasticity, arterial intima-media thickness (IMT), and high and low density lipoprotein-cholesterol (HDL-C, LDL-C).

ETS has been associated with a number of measurable physiological and biochemical changes in exposed individuals. These include increases in blood levels of atherogenic lipids and arterial wall thickness, decreases in aortic elasticity, endothelial responsiveness, blood levels of HDL-C and exercise endurance. It has also been associated with platelet activation and enhanced plaque growth. These effects are thought to be responsible, at least in part, for the increased risks of CHD, ischemic stroke and sudden death associated with exposure to cigarette smoke.

8.1. Description of Recent Studies

This section begins with a review of three meta-analyses relating the risks of CHD to ETS exposure in the home and/or workplace (He *et al.*, 1999; Law *et al.*, 1997; Wells, 1998). MI is the endpoint in the subsequent three studies by Rosenlund *et al.* (2001), Ciruzzi *et al.* (1998) and Sargent et al. (2004), while CHD is addressed by prospective studies by Enstrom and Kabat (2003) and Whincup et al. (2004). The possible role of ETS exposure in stroke is addressed by Zhang *et al*. (2005), Bonita *et al*. (1999) and You *et al*. (1999). These are followed by studies of the atherogenic effects of ETS in adults (Moffatt *et al.*, 2004), children (Moskowitz *et al.*, 1999), and mice (Gairola *et al.*, 2001). A series of studies of the relationship between endothelial properties and function, and cardiovascular risk provide a theoretical mechanistic basis to explain some of the associations between ETS exposure and CHD outcomes.

8.1.1. Coronary Heart Disease – Meta-analyses

Table 8.10 Summary of Cited Studies: Coronary Heart Disease – Meta-analyses

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments
He *et al.,* 1999	Meta-analysis of 18 epi studies of nonsmokers' risk of CHD from ETS 10 Cohort, 8 Case-control	 Men Women Cohort Case-control Work Home 1-19 cig/d > 20 cig/d	CHD incidence 1.22 (1.10; 1.35) 1.24 (1.15; 1.34) 1.21 (1.14; 1.30) 1.51 (1.26; 1.81) 1.11 (1.00; 1.23) 1.17 (1.11; 1.24) 1.23 (1.13; 1.34) 1.31 (1.21; 1.42)	Inconsistent confounder control. All controlled for age and sex. 6 cohort studies controlled for b.p./hypertension, weight/BMI, cholesterol or hyperlipidemia. In 10 studies with control for CHD risk factors, RR = 1.26 (1.16; 1.38; p<0.001). Dose-exposure increase in risk.
Wells 1998	Meta-analysis of workplace ETS and CHD in 8 studies 1,699 cases Appendix: Update of 1994 home exposure	Workplace Top 3 studies + next 4 + ACS All adult Tier 1 All studies Tier 1 All studies	RR for CHD 1.50 (1.12; 2.01) 1.35 (1.09; 1.67) 1.18 (1.04; 1.34) Morbidity 1.86 (1.20; 2.88) 1.49 (1.29; 1.78) Mortality 1.87 (0.56; 6.20) 1.23 (1.14; 1.32) Both 1.28 (1.20; 1.37)	Ranked studies by quality of ETS exposure data, then by control for confounders. Am. Cancer Society Study.
Law *et al*., 1997	Meta-analysis of 19 studies of ischemic heart disease in never- smokers living with vs without smoker. N=6,600 events	Men and Women + ETS Adj for diet	Ischemic heart disease risk 1.30 (1.22; 1.38) 1.23 (1.14; 1.33)	Estimated that diet alone of nonsmokers living with smokers increased risk 6%. Thus RR adjusted for diet is 1.30/1.06 = 1.23

He et al. (1999) conducted a meta-analysis of 18 epidemiological studies (10 prospective cohort, 8 case-control) relating ETS exposure and coronary heart disease (CHD). From these studies, overall nonsmokers exposed to ETS had a pooled relative risk (RR) of CHD of 1.25 (95% CI 1.17-1.32; p<0.001) compared to nonexposed nonsmokers. The cohort studies included Hirayama, 1990; Garland *et al.,* 1985; Svendsen *et al.,* 1987; Butler, 1988 (two-separate studies); Sandler *et al.,* 1989; Hole *et al.,* 1989; Humble *et al.,* 1990; Steenland *et al.,* 1996; and Kawachi

et al., 1997. The analysis by He *et al.* (1999) excluded three potentially relevant studies: Tunstall-Pedoe *et al.* (1995), because it was a cross-sectional survey; Layard (1995), as it did not provide valid data on passive smoking, and the case and control groups were not comparable; and LeVois & Layard (1995), the results of which conflicted with a "more careful" study by Steenland *et al.* (1996) of many of the same data from the American Cancer Society Cancer Prevention Study II (ACS-CPS-II).

In the cohort studies the outcome measure was MI or death due to CHD and the pooled RR for these outcomes was 1.21 (95% CI 1.14-1.30), with mean follow-up periods ranging from 6 to 20 years. The case-control studies included four that assessed ETS exposure from spouse and/or children (Lee *et al.,* 1986; He, 1989; La Vecchia *et al.,* 1993; Ciruzzi *et al.,* 1998) and another four that also included ETS exposure from work (Jackson, 1989; Dobson *et al.,* 1991; He *et al.,* 1994; Muscat & Wynder, 1995). In the case-control studies, the pooled estimated risk (odds ratio; OR) for diagnosis of CHD was higher at 1.51 (95% CI 1.26-1.81) than in the cohort studies. The RR was similar in men, 1.22 (95% CI 1.10-1.35), and women, 1.24 (95% CI 1.15-1.34). There was no significant difference between those exposed to ETS at home (1.17; 95% CI 1.11-1.24), or in the workplace (1.11; 95% CI 1.00-1.23). A dose effect was also suggested with the pooled RR for nonsmokers exposed to 1-19 cigarettes/day of 1.23 (95% CI 1.13-1.34), increasing to 1.31 (95% CI 1.21-1.42) with exposure to ETS from >20 cigarettes/day.

The main limitation of this work is that control for confounders and effect modifiers was inconsistent across studies. Age and sex were controlled in all cohort studies, but only six controlled for blood pressure or hypertension, weight or BMI, serum cholesterol or hyperlipidemia. However, the pooled risk estimate calculated from the 10 studies, case-control and cohort, that controlled for important CHD risk factors, was not much different (1.26; 95% CI 1.16-1.38; $p<0.001$), suggesting that the effects of confounding factors were minimal. In addition, He *et al.* found that different combinations of studies, which included only peer-reviewed studies or used death or MI as the outcome measure, or which eliminated an outlier study, gave similar pooled RRs in the range of 1.24-1.26. In all cases the ETS effect was significant ($p<0.001$).

Wells, 1998. Most studies of passive smoke exposure focus on the home environment. However, for many people, the workplace is a significant source of exposure. Wells (1998) evaluated seven studies that addressed the pooled relative risks (RR) of CHD from workplace ETS exposure primarily on the quality of the passive smoking history (duration, intensity and frequency) and secondarily on the extent of adjustment for various confounders. The top three studies were He *et al.* (1994); Kawachi *et al.* (1997); and Butler (1988), from which Wells estimated a RR for CHD of 1.50 (95% CI 1.12-2.01) for both sexes combined. The next four studies had less extensive control for confounders, and less information on data sources (surrogates vs direct interviews) and smoking history. Inclusion of these studies brought the RR down to 1.35 (95% CI 1.09-1.67). Inclusion of the study by Steenland *et al*. (1996), with its relatively poor workplace exposure data, brought the combined RR to 1.18 (95% CI 1.04-1.34). Even at this level, there was a statistically significant risk of CHD from workplace ETS exposure that is similar to the RRs reported for home ETS exposure, a similarity also observed by He *et al.* (1999). Thus, using the studies with better quality exposure estimates resulted in increased RR reported for ETS exposure and CHD. This effect is reflected in the appendix to Wells' paper which included seven more-recent studies not used in the original analysis. From the combined studies, the pooled risk for CHD morbidity for all adult exposure was 1.49 (95% CI 1.29; 1.78). This estimate increased to 1.86 (95% CI 1.20; 2.88) when only tier 1 studies were used. Similarly for CHD mortality, the estimate from all studies was 1.23 (95% CI 1.14; 1.32), and 1.87 (95% CI 0.56; 6.20) for tier 1 only studies.

The potential for confounding by diet is diminished in workplace exposure studies as coworkers are less likely to share the same dietary habits as are people living in the same household. The similarity in the RRs associated with home and work ETS exposure thus suggests that while dietary effects cannot be excluded, dietary effects alone cannot explain the excess CHD risk.

This analysis excluded LeVois and Layard's (1995) study of ACS CPS-I data due to uncertainty about the selection of subjects in favor of the "more detailed analysis" by Steenland *et al* (1996) of the ACS CPS-II data. Layard's 1995 study based on the National Mortality Followback Survey was also excluded as it contained a disproportionate number of blacks, Native Americans and young people who had died of ischemic heart disease. ETS exposure was reported by spouses or surrogates on mailed questionnaires rather than from direct interviews. With the

inclusion of Layard's data, the combined RR for mortality dropped from 1.23 to 1.17 (95% CI 1.10-1.25). For combined morbidity and mortality, the risk dropped from 1.28 to 1.22 (95% CI 1.15-1.29); however it is not clear how these numbers were derived. Brown (1998) and Glantz and Parmley (1996) pointed out a number of other reasons for excluding the analysis by LeVois and Layard (1995), in favor of the analysis by Steenland *et al*. (1996) of the updated data.

Law et al. (1997) conducted a meta-analysis of 19 published studies of the risk of ischemic heart disease in never-smokers living with smokers versus with nonsmokers. Also included were five large prospective studies of active smoking and ischemic heart disease, studies of smoking and platelet aggregation, and studies relating smoking and diet. They derived a relative risk of ischemic heart disease at age 65 for ETS exposure of 1.30 (95% CI 1.22-1.38; $p<0.001$), similar to the extrapolated risk at age 65 from smoking one cigarette a day: 1.39 (95% CI 1.18-1.64; $p<0.001$). From cohort studies in which diet was evaluated, dietary differences between nonsmokers who lived with a smoker versus those who did not were estimated to account for an excess ischemic risk of 1-2%. Thus, adjusted for diet, specifically a lower consumption of fruits and vegetables in smoking households, the passive smoker's risk of developing ischemic heart disease dropped to 1.23 (95% CI 1.08; 1.40). Summary estimates were similar for men and women in both cohort and case-control studies.

Platelet aggregation has been suggested as a plausible mechanism to account for the disproportionate risks of CHD associated with ETS versus active smoking. Law *et al.* (1997) reviewed data from the Caerphilly collaborative heart disease study (Elwood *et al.,* 1991) and found a linear association between the risk of ischemic heart disease and platelet aggregation. It was estimated that an increase of one standard deviation (SD) in platelet aggregation (as measured by an increase in optical density) was associated with a relative risk of 1.33 (95% CI 1.19-1.48; $p<0.001$). However, the SDs associated with the relative risk estimates were relatively large. From another series of studies comparing platelet aggregation in non-, passive- and active-smokers, ETS exposure resulted in an increase in platelet aggregation of 1.03 SD while active smoking caused an increase of 1.25 SD. Based on the linear relationship mentioned above this translates into an associated immediate relative risk of ischemic heart disease of 1.34 (95% CI 1.19-1.50) for passive smokers and 1.43 (95% CI 1.24-1.63) for active smokers. While smoke exposure alters platelet sensitivity to aggregation-inducing or inhibiting compounds, and

altered platelet aggregation is associated with an immediate risk of IHD, platelet aggregation *per se* does not appear predictive of long-term ischemic risk (Elwood *et al.,* 2001).

This meta-analysis excluded a study by Layard (1995), which found no increased risk of ETS from spousal smoking. However Layard included ever-smoking versus using only current-smoking spouses. In the larger studies, risk estimates from exposure to current-smoking spouses tend to be higher than from ever-smokers as the latter group includes ex-smokers. Based on these studies of ETS, and also on parallel observations in active smokers (Benowitz, 2003), it appears that the adverse cardiovascular impacts of tobacco smoke exposure are considerably (although not necessarily completely) reversed within a few years of cessation of exposure, so the cessation of exposure to ETS in the spouses of ex-smokers reduces their risk. These three meta-analyses analyzed substantially the same set of studies and derived similar overall statistically significant estimates of risk for CHD from ETS exposure of 1.23-1.26. Subanalyses of the studies deemed to have better confounder control and/or ascertainment of exposure resulted in higher risk estimates.

8.1.2. Coronary Heart Disease – Primary Studies

Table 8.11 Summary of Cited Studies: Coronary Heart Disease – Primary Studies

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Whincup *et al.*, 2004 Britain	Prospective study of serum cotinine and risk of CHD and stroke n = 4729	Cotinine ≤ 0.7 ng/ml 0.8-1.4 “ 1.5-2.7 “ 2.8-14.0 “ Smoker 1-9 cig/day ≤ 0.7 ng/ml 0.8-1.4 “ 1.5-2.7 “ 2.8-14.0 “ Smoker 1-9 cig/day	CHD HR all men 1.0 1.45 (1.01; 2.08) 1.49 (1.03; 2.14) 1.57 (1.08; 2.28) Trend p = 0.001 1.66 (1.04; 2.68) Never smokers 1.0 1.54 (0.88; 2.69) 1.89 (1.05; 3.99) 1.67 (0.91; 3.07) Trend p = 0.001 2.05 (1.14; 3.69)	Significant risk of CHD with increasing cotinine for all men (including former smokers). Trend still significant after elimination of former smokers. Risk of stroke not significantly associated with cotinine levels.

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Chen *et al.,* 2004	Cross-sectional study of ETS and CHD based on questionnaires n = 1,854 adults	Passive by self-report	Trend with ETS Angina $p < 0.01$ Undiag CHD $p < 0.05$ Diag CHD $p < 0.01$	Self-report ETS exposure associated with significant trends in increasing angina, diagnosed and undiagnosed CHD. Serum cotinine not well correlated.
Sargent *et al.*, 2004	Observational case study of effect of smoking ban on AMI incidence	Public ETS During ban Other years OR difference	Avg #AMI 24 40 -16 (-31.7; -0.3)	AMI incidence significantly lower during 6 month smoking ban vs before or after.
Enstrom and Kabat 2003	Prospective cohort study of ETS and CHD deaths in CPS-I. 35,561 never smokers	Spousal ETS ever ETS Cig/day 1-9 10-19 20 21-39 ≥ 40	CHD death 0.94 (0.85; 1.05) Male CHD death 0.98 (0.78; 1.24) 0.82 (0.66; 1.02) 0.89 (0.70; 1.13) 1.13 (0.76; 1.68) 1.24 (0.70; 2.19)	Suggestion of exposure-response for death by CHD in men but not women. Effect not statistically significant for either gender.
Rosenlund *et al.,* 2001 Sweden	Rated risk of MI from ETS at work and/or from spouse in 45-70 yr olds. 344 nonfatal MI, 677 pop controls	Spouse < 20 cig ≥ 20 cig wrk+spouse 0-17 hr-yr 18-41 hr-yr 42-89 hr-yr > 90 hr-yr after ETS stop > 16 yr 7-16 yr 1 - 6 yr < 1 yr	OR for MI 1.02 (0.73; 1.42) 1.58 (0.97; 2.56) 0.70 (0.43; 1.15) 1.22 (0.80; 1.88) 1.27 (0.83; 1.95) 1.55 (1.02; 2.34) 0.92 (0.58; 1.44) 1.11 (0.70; 1.74) 1.30 (0.85; 1.98) 1.39 (0.91; 2.10)	ETS exposure associated with MI. Risk increased with dose (# cigs) from spouse and with duration (hr-yrs) from work and spouse. Increased time since cessation of ETS exposure reduced risk. Adjusted for age, BMI, sex, SES, job strain, hypertension, diabetes, diet. Inclusion of previous smokers as never smokers may explain lack of statistical significance.
Ciruzzi *et al*., 1998 Argentina	Case-control study of home ETS and acute MI. 336 never smokers with first MI vs 446 never smokers without.	1 relative smoked men women both	OR for AMI 1.89 (1.13; 3.18) 1.54 (0.95; 2.51) 1.68 (1.20; 2.37)	Compared ETS of nonsmokers hospitalized for 1st MI vs those hospitalized for non-cardiac disease.

*Abbreviations: AMI – acute myocardial infarction; BMI – body mass index; CHD – coronary heart disease; OR – odds ratio; SES – socioeconomic status.

Whincup et al. (2004) conducted a population-based prospective study of the effects of passive smoking on the risks of coronary heart disease (CHD) and stroke. Questionnaires administered at baseline in 1978-80 provided data on current and past smoking habits, alcohol intake, physical activity, and medical history. At baseline, blood pressure was recorded and blood taken for determination of total and HDL cholesterol, and serum cotinine. Cotinine levels were determined by gas-liquid chromatography with a detection limit of 0.1 ng/ml. Questionnaire data and blood analyses were available for 4,729 men. During the 20-year follow-up, all cause mortality and cardiovascular morbidity were recorded. At baseline, men who reported that they did not smoke tobacco products and who had serum cotinine levels < 14.1 ng/ml were considered current nonsmokers. Among these, those who reported never smoking tobacco products were considered lifelong non-smokers. Light active smokers were those reporting smoking 1-9 cigarettes per day irrespective of cotinine levels. Smoking habits were assessed again at five and twelve years after baseline by postal questionnaire.

Cox proportional hazard models were used to assess the association between serum cotinine and cardiovascular disease risk. The relative hazard estimates were stratified by town of residence and adjusted for age, BMI, height, systolic and diastolic blood pressure, serum total and HDL cholesterol, white cell count, FEV_1, triglyceride levels, physical activity, alcohol intake, social class, diabetes, pre-existing CHD, and cigarette smoking history. As shown in Table 8.12, among all participants, cotinine levels were significantly associated with CHD risk. These risk estimates were only slightly affected by adjustment for the risk factors listed above compared to adjustment for age alone. There was also a significant dose-response association between increasing cotinine levels and increasing risk of CHD. After exclusion of former smokers, risk estimates were still elevated, but with wider confidence intervals ; in two of the four categories the effect was not statistically significant. There was no statistically significant association between cotinine levels and incidence of stroke.

Table 8.12 Serum Cotinine and Cardiovascular Disease Risk (hazard ratio) (Whincup *et al.*, 2004)

	Cotinine (ng/ml) HR (95% CI)				Smokers	Trend
CHD	≤ 0.7	0.8-1.4	1.5-2.7	2.8-14.0	1-9/day	P
All men[a]	1.0	1.50 (1.06; 2.12)	1.56 (1.11; 2.20)	1.61 (1.15; 2.27)	1.65 (1.08; 2.54)	0.001
All men[b]	1.0	1.45 (1.01; 2.08)	1.49 (1.03; 2.14)	1.57 (1.08; 2.28)	1.66 (1.04; 2.68)	0.001
No former smokers[a]	1.0	1.32 (0.78; 2.25)	1.44 (0.83; 2.50)	1.55 (0.90; 2.69)	1.17 (1.07; 2.96)	0.006
No former smokers[b]	1.0	1.54 (0.88; 2.69)	1.89 (1.05; 3.99)	1.67 (0.91; 3.07)	2.05 (1.14; 3.69)	0.001
Stroke						
All men[a]	1.0	0.76 (0.44; 1.31)	0.83 (0.50; 1.40)	0.87 (0.52; 1.47)	1.48 (0.81; 2.69)	0.73
All men[b]	1.0	0.83 (0.46; 1.47)	0.94 (0.54; 1.64)	0.77 (0.42; 1.41)	1.45 (0.71; 2.96)	0.99
No former smokers[a]	1.0	1.01 (0.43; 2.35)	0.66 (0.25; 1.78)	1.25 (0.54; 2.89)	1.95 (0.90; 4.22)	0.52
No former smokers[b]	1.0	1.34 (0.53; 3.40)	1.39 (0.48; 4.04)	2.16 (0.80; 5.80)	2.69 (1.07; 6.75)	0.11

[a]Stratified by town and adjusted for age. [b]Stratified by town and adjusted for all covariates.

Risk estimates were calculated for consecutive five-year intervals of the follow-up. As shown in Table 8.13, there appears to be an attenuation of CHD risk over time. Since cotinine levels were only determined for baseline, it is uncertain what the true ETS exposures were after baseline. It is likely that this decline is in part a reflection of the general decline in smoking in Britain during the follow-up period. This suggests that basing risk estimates on the baseline ETS exposures may underestimate the risk if subsequent exposures are lower.

Table 8.13 Change in CHD Risk Over Study Period (Whincup *et al.*, 2004)

	Follow-up Period (years) HR (95% CI)			
Exposure	**0-4**	**5-9**	**10-14**	**15-20**
Passive	3.73 (1.32; 10.58)	1.95 (1.09; 3.48)	1.13 (0.63; 2.04)	1.04 (0.62; 1.76)
Active	3.32 (0.87; 12.64)	1.66 (0.66; 4.18)	1.71 (0.71; 4.10)	1.34 (1.23; 1.47)

The follow-up questionnaires at five and twelve years indicated that non-smokers at baseline continued to report a non-smoking status. When former smokers were excluded from the analysis, the risk estimates, while still elevated, included no effect. This is likely due in part to the reduced size of the remaining group. It may also reflect a residual higher risk for CHD among former smokers versus never-smokers, a risk possibly exacerbated by ETS exposure. Overall, this study supports a significant association between ETS exposure and CHD.

Chen et al., 2004. In this cross-sectional study, data from the Scottish MONICA surveys in 1986, 1989, 1992, and 1995 were analyzed to determine whether prevalent heart disease (CHD) was independently associated with ETS exposure as measured by self-report, serum cotinine, and the two measures combined. Data on sociodemographics, personal health, diet and exposure to tobacco smoke were collected by questionnaire for 1,854 subjects. Electrocardiograms (ECG) and blood samples for cotinine levels and other biochemical assays were collected during clinical examinations. The study examined the effects in nonsmokers defined by self-report and serum cotinine levels below 17.50 ng/ml. Probable angina and undiagnosed CHD were apparently determined from responses to the questionnaires.

The prevalence of angina showed a dose-response with increasing self-reported exposure to ETS (p for trend < 0.01). The 300 cases of undiagnosed CHD further showed a dose-response relationship with ETS exposure (p for trend < 0.05) with a significant OR only at the highest exposure level (1.6, 95% CI 1.0; 2.5). When all CHD categories (angina, undiagnosed CHD and diagnosed CHD) were combined, there was a significant dose-response trend (p < 0.01). However, serum cotinine did not completely corroborate self-report. For example, there was a higher prevalence of angina, undiagnosed CHD and all CHD in subjects with no detectable cotinine compared to those with cotinine levels >0-1.05 ng/ml. (However, the prevalence of diagnosed CHD was lowest in the group with no detectable cotinine). This unexpected result may reflect active avoidance of ETS exposure by individuals who are aware of their CHD condition. Alternatively, since the lower limit of detection of the assay for cotinine was not specified, a lack of sensitivity in the assay may have limited the ability to associate cotinine levels with CHD outcomes. The serum cotinine level of 17.50 ng/ml used to distinguish active from passive smokers is higher than in most other studies, so some light active smokers may have been included in the nonsmoking group. Among those with detectable continine, there was a dose-response in the categories of questionnaire angina, undiagnosed CHD, and all CHD.

Given the apparent limitations of the cotinine assay and the high cotinine level used to separate nonsmokers from smokers, the results of this study are viewed as suggestive of an association between ETS exposure and CHD.

Sargent et al. (2004) studied the effects of a six-month smoke-free policy in public and work places on the incidence of hospital admissions for acute myocardial infarction (AMI) in Helena, Montana. Data on AMI were derived from discharge records of the only hospital that provided cardiology services to Helena and the surrounding area. Diagnoses were made or confirmed by physicians blinded to the study, and included both primary and secondary diagnoses of AMI. Overall, 304 cases were included. Admissions during the six months the ban was in effect were compared with those during the same six months of the previous and following years, and from within versus outside of Helena, where the smoking ban was not in force.

During the ban, the number of admissions for AMI compared to the previous and subsequent years was significantly lower (24 vs an average of 40). At the same time, there was a non-significant increase in the number of admissions from outside the area of the ban (18 vs an average of 12.4). Admissions from within the area of the smoking ban were thus significantly lower than from the area without the ban.

Table 8.14 Effect on Admissions for Acute Myocardial Infarction (Sargent *et al*., 2004)

	Helena	**Outside Helena**
Ban year (2002)	24	18
Other years (avg)	40	12.4
Difference (95% CI)	-16 (-31.7; -0.3)	5.6 (-5.2; 16.4)
Difference Helena vs outside	-21.6 (-40.6; -2.6)	

The implementation of this ban created a geographically and temporally isolated experiment on the effects of smoke exposure on cardiovascular disease, the results of which indicate a significant adverse effect. However the study population was small and the number of AMI cases correspondingly low thus limiting the statistical power of the study and the ability to generalize the results. In addition, the non-randomized nature of the study leaves open the possibility of undetected systematic bias or confounding. Of the AMI cases, 38% were current smokers, 29% were former-smokers, and 33% were never-smokers. Thus it is not clear what proportion of the decrease in AMI admissions represents decreased smoking among active smokers versus curtailment of passive exposure among non-smokers. However, it does appear that cessation of smoke exposure had a positive effect on cardiovascular health.

Enstrom & Kabat (2003) examined ETS exposure and long-term mortality from CHD, lung cancer and chronic obstructive pulmonary disease (COPD) in a prospective cohort study of adult Californians enrolled in 1959 in the American Cancer Society's Cancer Prevention Study (CPS-I). Never smokers married to current or former smokers were compared to never smokers married to never smokers, with the former group subdivided based on the smoking status of the spouse (1-9, 10-19, 20, 21-39, ≥ 40 cigarettes per day). Former smokers were considered in a separate category. The relative risk of death was calculated as a function of the spouse's smoking status and adjusted for age and seven potential confounders at baseline: race, education, exercise, BMI, urbanization, fruit or fruit juice intake, and health status (good, fair, poor, sick).

For CHD among males, there was a suggestion of an exposure response based on ETS from increasing numbers of cigarettes smoked per day by the spouse but the confidence intervals included no effect (Table 8.11). Among women there was no evidence of an effect of spousal smoking as the reported risks were generally below unity.

There are several concerns with this study which are described in the review of Enstrom and Kabat in Section 7.3.2.1. There is potential misclassification of smoke exposure due to the high prevalence of cigarette smoking and thus extensive ETS exposure regardless of spousal smoking status at the start of CPS-I. Defining ETS exposure based solely on spousal smoking during the first third of the study period seriously biases the results towards the null. As a result, the control group, defined as non-ETS-exposed based on the absence of spousal smoking, would include individuals with extensive ETS exposure outside the home, at work and elsewhere.

Analyses were adjusted for the factors listed above at baseline; while race, education, exercise, weight, height, and fruit intake reportedly changed little over time, changes in health status or in other lifestyle factors that could affect survival were not included in the adjustment. There was, for example, a large increase between 1959 and 1999 in the proportion of the population using vitamin pills (38.3% and 81.2%, respectively) that may have mitigated the effects of smoke exposure. Finally, the category of current smokers may include intermittent smokers and those who started smoking relatively recently, potentially leading to wide variations in the duration of ETS exposure among never smokers, and a dilution of effects. Thus, while this study does not

appear to support a causal role for ETS in CHD mortality, the problems noted above lead to difficulty in interpretation of the results.

Rosenlund et al. (2001) evaluated the risk of myocardial infarction (MI) associated with ETS exposure at work and/or from spousal smoking among participants in the Stockholm Heart Epidemiology Program (SHEEP). Data from 334 non-fatal never-smoking MI cases and 677 population controls ages 45-70 yrs (avg 62.6 ± 6.6 yrs) in Sweden were collected by postal questionnaire and telephone follow-up. The collected data included ETS exposure, age, gender, body mass index (BMI), socioeconomic status, job strain, hypertension, diet and diabetes. The odds ratios (OR) for MI after adjustment for these factors (sexes combined) showed an exposure-response relationship with the number of cigarettes smoked by the spouse. The risk of MI from combined ETS exposure from work and spouse, expressed in hour-years, also showed an exposure-response relationship. (1 hour-year = 365 hrs or the equivalent exposure duration of one hr/d for one year.) In addition, there was a higher risk from recent exposure, which decreased with increasing years since last exposure at home or work (Fig. 8.01).

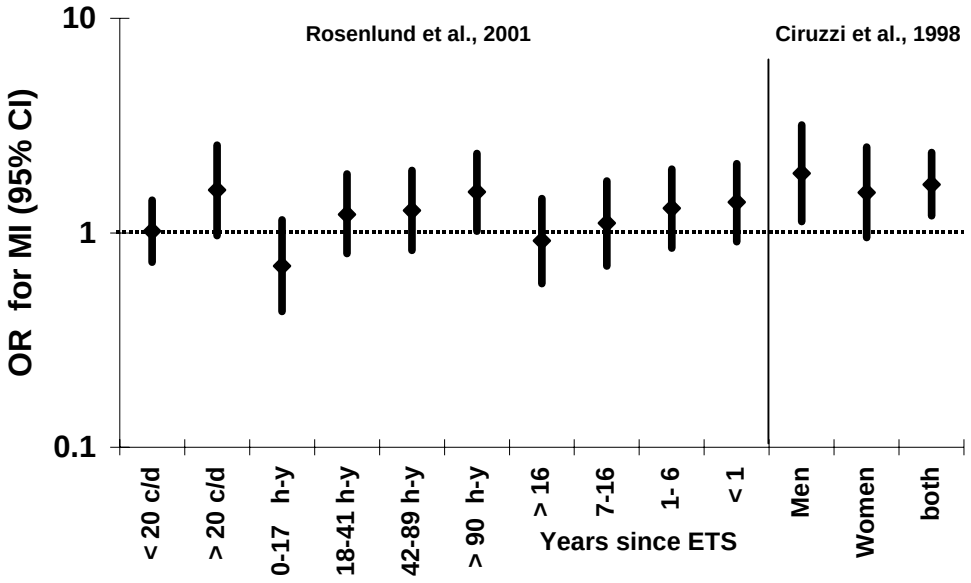
Except at the highest exposure duration, the confidence intervals reported include no effect. However, this study defined never smokers as "…subjects who had never smoked regularly for at least a year…". As a result, the control group may have included previous smokers and people who smoke intermittently, the inclusion of whom might tend to diminish any apparent effects due to ETS exposure and make the OR estimates artificially low.

The participation rate in the SHEEP study was relatively high (≥ 70%) thus minimizing bias due to nonparticipation and differential reporting. Exposure misclassification is also expected to be minor based on data from population validation studies of reported smoking that indicate about 5% misclassification of ever-smokers in the never-smoking category, mainly of light or long-term ex-smokers. The misclassification rate was even lower in case-control studies in which 1.25% of "never-smokers" were reported by next of kin to be former regular smokers (Nyberg *et al.,* 1998; 1997). In the Rosenlund *et al.* study, recall bias was further minimized by excluding fatal MI cases.

It has been argued that the association between ETS exposure and CHD may be explained by differences in the diets of smoking versus nonsmoking families (Forastiere *et al.,* 2000). To

address this concern, Rosenlund *et al.* (2001) adjusted for dietary intake of fat and fiber. This adjustment reportedly did not affect the results. Similarly, dietary cholesterol and blood lipids were considered and reportedly had little or no effect on the analysis.

Figure 8.01 Two Studies of the Risk of Myocardial Infarction in Relation to ETS Exposure



Ciruzzi et al. (1998) conducted a case-control study of the association between exposure to ETS in the home and the risk of acute myocardial infarction (AMI) conducted from 1991-1994 in Argentina. Cases included 336 never-smokers (median age 66) admitted to hospitals for first episodes of AMI. Those with a history of ischemic heart disease, valvular disease, cardiomyopathy or cardiac surgery were excluded. Controls comprised 446 never-smokers, with a median age of 65, admitted to the same hospitals for acute conditions unrelated to known or suspected risk factors for AMI. Data were collected during interviews on age, gender, education, diet, alcohol and coffee consumption, socioeconomic status, BMI, presence of diabetes and hypertension, family history of MI, and smoking habits of spouse and children. Serum cholesterol was determined following hospital admission. Odds ratios were calculated for AMI from multiple logistic regression analyses adjusted for these factors. For men, the OR for AMI when at least one person in the household smoked was 1.89 (95% CI 1.13-3.18), for women 1.54 (95% CI 0.95-2.51), and for both sexes, 1.68 (95% CI 1.20-2.37) (Fig. 8.01). For women, an exposure-response trend with spousal smoking was suggested. An OR of 0.90 (95% CI 0.28-

2.86) for spousal smoking of 1-20 cigarettes per day increased to 3.31 (95% CI 0.77-14.17) at >20 cigarettes per day.

The participation rate was high (96%) with good comparability of the recruitment areas for cases and controls. However, while the median ages of both groups were similar, a higher percentage of the cases was over 75 years of age compared to the control group (28.6% vs 17.7%), which may have exaggerated the ETS effect. Since the cases and controls for this study were admitted to hospitals for AMI or other conditions, the applicability of these results to an otherwise healthy population may be limited. Indeed, the authors found evidence that interaction between ETS exposure and chronic conditions may influence risk for CHD and AMI. The OR for AMI when at least one relative smoked rose from 1.51 (95% CI 1.04-2.19) in the absence of diabetes, to 5.26 (95% CI 2.44-11.36) in its presence. Similarly, hypertension increased the OR associated with ETS from 1.65 (95% CI 1.03-2.65) to 3.28 (95% CI 2.02-5.34), while with hypercholesterolemia the OR went from 1.60 (95% CI 1.08-2.34) to 4.01 (95% CI 2.17-7.40). A family history of MI was found to enhance the ETS effect with ORs increasing from 1.71 (95% CI 1.16-2.53) to 4.08 (95% CI 2.16-7.70). This study thus suggests that individuals with other risk factors for AMI may be especially susceptible to the effects of ETS exposure.

8.1.3. Stroke

Few studies address the possible association of passive smoking with stroke. The three studies described below all demonstrated significant elevations in risk of stroke and two of the studies provide evidence for a dose-response. In addition, one of the studies demonstrated a stronger odds ratio for stroke in active smokers when passive smokers are removed from the referent group. Take together these studies provide evidence suggesting a role for ETS in stroke. Limitations in the studies are described below. Further investigation is warranted to clearly elucidate the role of ETS exposure in stroke.

Table 8.15 Summary of Cited Studies: Stroke

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Zhang *et al*., 2005 China	Population-based cross-sectional study of stroke in women with spousal ETS. n = 22,982	Amount 1-9 cig/d 10-19 cig/d ≥ 20 cig/d Duration ≤ 17 yrs > 17 yrs Pack-years ≤ 13 pk-yrs > 13 pk-yrs	Stroke OR 1.28 (0.92; 1.77) 1.32 (1.01; 1.72) 1.62 (1.28; 2.05) trend p=0.0002 1.13 (0.70; 1.82) 1.47 (1.22; 1.78) trend p=0.0004 1.12 (0.82; 1.54) 1.55 (1.27; 1.90) trend p<0.0001	Adjusted for age, education, SES, alcohol, BMI, medical history, menopausal status. Significant risk and dose response trends. Study limited to women 40-70 yrs old.
Bonita *et al.,* 1999 New Zealand	Population-based, case-control study of stroke vs smoking status. Stroke: men 279, women 242. Ctrl: 1,851. 5-74 yr	Status: Non (ns) Men ns Women ns Smoker vs ns +/-ETS ns-ETS	Stroke OR 1.82 (1.34; 2.49) 2.10 (1.33; 3.32) 1.66 (1.07; 2.57) 4.14 (3.04; 5.63) 6.33 (4.50; 8.91)	Adjusted for age, sex, heart disease, hypertension (not diet). Source of ETS not delineated. Higher OR for stroke in men. Exclusion of ETS-exposed non-smokers (ns) in reference group increases smokers' OR.
You *et al*., 1999 Australia	Case-control study of ischemic stroke in ex, never, current smokers living with vs. without smoker n = 452	Spouse: Ever 1-20 cig/d ≥ 20 cig/d Ever 1-20 cig/d ≥ 20 cig/d	OR: NS group 1.70 (0.98; 2.92) 1.55 (0.83; 2.88) 1.91 (0.94; 3.88) Whole group 2.03 (1.33; 3.10) 1.72 (1.07; 2.77) 2.59 (1.51; 4.47)	452 cases of first time ischemic stroke vs. age-, sex-matched ctrl. Incl. current, ex, never smokers, parental & spousal exposure. Adj for smoking status, heart disease, hypertension, diabetes, education.

Zhang et al. (2005) examined the prevalence of stroke among non-smoking Chinese women exposed to spousal smoking. This cross-sectional study used baseline data from The Shanghai Women's Health Study, a population-based cohort study in China. Data on demographics, lifestyle, medical history, and husband's smoking habits were collected by structured interview on 60,377 women, 40-70 years of age. Multivariate analyses were adjusted for age, education,

occupation, income, alcohol consumption, BMI, exercise, menopausal status, diabetes, hormone therapy and medication use. No distinction was made between ischemic and hemorrhagic stroke.

As seen in Table 8.16, the adjusted OR for stroke was elevated by ETS exposure, significantly so with higher or longer exposures. There were also significant exposure-response trends for both degree and duration of exposure (Fig. 8.02).

Table 8.16 Spousal ETS and Stroke Risk (Zhang *et al*., 2005)

Exposure	Cases/total	OR (95% CI)	P for trend
Cigarettes/day			
1-9	46/6,736	1.28 (0.92; 1.77)	
10-19	77/11,233	1.32 (1.01; 1.72	
≥ 20	116/14,316	1.62 (1.28; 2.05	0.0002
Duration (yrs)			
≤ 17	25/16,245	1.13 (0.70; 1.82)	
> 17	214/16,042	1.47 (1.22; 1.78)	0.0004
Pack-years			
≤ 13	54/16,512	1.12 (0.82; 1.54)	
> 13	185/15,772	1.55 (1.27; 1.90)	<0.0001

Exposure was based on living with a smoking husband and so missed other sources of ETS exposure. In addition, the exposure assessment was only made at baseline and so does not reflect any subsequent changes in smoking habits. These two effects would be expected to lead to an underestimate of the association with passive smoking. In addition to being population-based, this study had the advantages of large sample size and high participation rate (92.7%). The elevated risk estimates and dose-response trends indicate a significant association between exposure to ETS and stroke in women.

Bonita et al. (1999) conducted a population-based case-control study of smoking status versus stroke incidence in first-time stroke victims (279 men, 242 women) compared with 1,851 controls. Cases were taken from the Auckland stroke study, which documented stroke events among the Auckland population in 1991-1992. Trained nurse interviewers administered questionnaires to the stroke victims, or to next-of-kin if the patient had died, to assess age, gender, history of smoke exposure, heart disease, hypertension and diabetes. The risks for stroke among active smokers were derived from comparisons with never-smokers with and without ETS exposure and with never-smokers with no ETS exposure. Active smokers were separated

into three groups for analysis based on the number of cigarettes smoked per day (≤ 5, 6-14, ≥ 15). Ex-smokers were included and grouped according to the time elapsed since quitting (< 2, 2-10, >10 yrs). A person was classified as ETS-exposed if a household member had regularly smoked cigarettes in their presence or if a co-worker smoked in their presence for more than one year during the prior ten years.

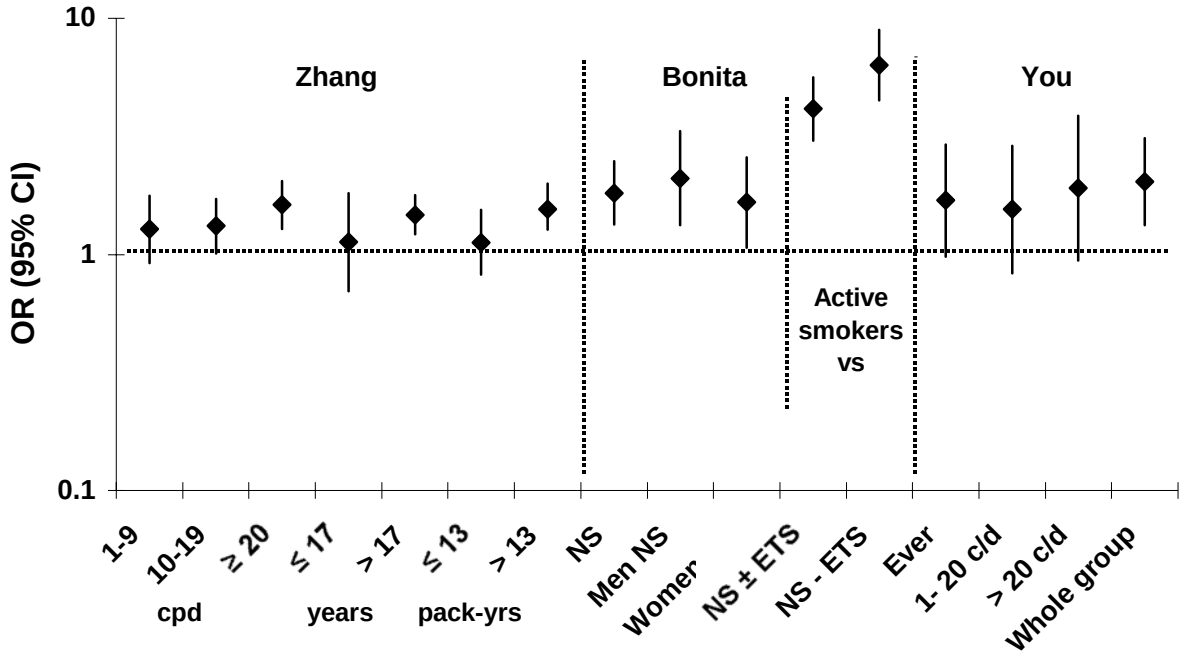
After adjustment for heart disease, hypertension, diabetes, age and sex, ETS exposure among never-smokers was associated with an elevated risk of stroke (OR 1.82; 95% CI 1.34-2.49), which was higher in men (OR 2.10; 95% CI 1.33-3.32) than in women (OR 1.66; 95% CI 1.07-2.57). Compared to all nonsmokers, the risk of stroke for active smokers was high (OR 4.14; 95% CI 3.04-5.63). More importantly, when the reference group included only nonsmokers with no ETS exposure, the OR for stroke among active smokers increased to 6.33 (95% CI 4.50-8.91). This additionally supports an ETS effect in stroke and underscores the importance of reference group selection (Fig. 8.02).

One of the strengths of this study is that all strokes in the Auckland population, fatal and nonfatal, were identified, though there was no differentiation of stroke type or severity in the analysis. The decision to include all nonfatal and fatal cases is important, as passive smoke exposure may be associated with strokes of varying severity from mild to fatal. On the other hand, it limits the study's ability to discern whether ETS exposure is associated with stroke severity.

Limitations of this study include the lack of control for diet. Reporting bias may have resulted from the fact that cases and controls were interviewed in separate years, allowing for exposure to other factors in the intervening time. Also controls were interviewed directly while data for some cases were obtained from a caregiver or next-of-kin. Data on education and socioeconomic status were not included, as 60% of the patients with acute stroke were past retirement age (65-74 yrs). The authors attempted to reduce confounding due to socioeconomic factors by excluding Maoris and Pacific Islanders who tend to be of lower socioeconomic status, and have higher smoking and stroke rates than those of European descent. There may have been incomplete control for age in this study. since more than half the cases, but only about half of the controls were 55 and older. The reliability of self-reported ETS exposure was not verified

biochemically, so it is possible that stroke victims and healthy controls reported smoking consumption differently. To mitigate this potential bias, questions regarding smoke exposure were embedded among a large number of other questions.

Figure 8.02 Three Studies of the Risk of Stroke and ETS Exposure



You et al. (1999) conducted a case-control study in Australia of ischemic stroke in 452 never, former, and current smokers living with smokers compared with a similar number of age and sex-matched neighborhood controls not exposed to ETS. The study group was 59.5% male with a mean age of 59 (SD ± 14.8) years. Parental and spousal smoking were examined but the former had no effect on stroke risk. Among never-smokers exposed to spousal ETS, the odds ratios adjusted for age, gender, hypertension, ischemic heart disease, diabetes, personal smoking and education, were elevated and suggested an exposure-response, but the 95% CIs included unity, consistent with an estimate of no increased risk. However, since ETS exposure was only assessed as exposure to a smoking spouse, the reference group likely included individuals with ETS exposure from other sources, thus weakening the apparent association. On the other hand, the risk for ischemic stroke from spousal smoking for the entire group, including smokers as well as nonsmokers, was significantly elevated with an adjusted OR of 2.03 (95% CI 1.33; 3.10) (Fig 8.02). This suggests that smokers may also be susceptible to ETS. Indeed, when the data for

active smokers was stratified according to smoking by the spouse, the OR for stroke for active smokers exposed to spouse's ETS was 1.91 (95% CI 0.90; 4.04) (data not plotted).

Because this was a hospital-based study, selection bias is a concern, especially since the controls were recruited from the community rather than from the hospital. In addition, recruitment occurred in two phases, from 1985 to 1988, and from 1988 to 1992. The latter group contained patients ≤ 55 years of age. Recognizing these weaknesses, the authors suggest that these results, although indicating an association between ETS and stroke, should be regarded as hypothesis generating.

8.1.4. Impaired Vascular Function and Other Pathophysiological Effects in Humans

Studies examining the pathophysiological effects of ETS exposure on the vascular system and blood in humans are described below. The changes described lead to chronic heart disease and can precipitate or aggravate an acute event (e.g., myocardial infarction).

Table 8.17a Summary of Cited Studies: Vascular Pathophysiological Effects- Humans.

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Mack *et al.,* 2003	Cross-sectional study of passive smoking and arterial stiffness n = 227 adults	Passive BMI >27.1 Age ≥ 55 IMT > 0.707 BMI >27.1 IMT > 0.707	Stiffness increase w/#ETS sources trend p = 0.048 trend p = 0.09 trend p = 0.05 w/ hours of ETS trend p = 0.04 trend p = 0.04	Significant trends of increasing arterial stiffness with number of sources and number of hours of ETS exposure among persons with high BMI, larger IMT, and older age.
Otsuka *et al.,* 2001 Japan	Measured CFVR (coronary flow velocity reserve) by Doppler echocardiography in active and passive smokers before and after 30 min passive smoke.	Nonsmokers Smokers Nonsmokers Smokers	Mean CFVR Before ETS 4.4 ± 0.91 3.6 ± 0.88 p = 0.02 After 30 min ETS 3.4 ± 0.73 p < 0.001 3.3 ± 0.74 p = 0.83	Passive smoke sig. reduced CFVR in nonsmokers and to same level as in active smokers. No sig differences between groups in age, heart rate, b.p., cholesterol, triglycerides and HDL. 15 smokers, 15 non-smokers, men, 27± 4 yrs
Pope *et al*., 2001	Measure heart rate variability (HRV) with ETS.16 adults.	2 hr ETS in smoking room	SDNN negatively correlated with ETS (p < 0.05)	Short exposure to ETS decreased HRV, a risk factor for chronic heart disease.
Woo *et al.,* 2000 China Australia	Tested vascular reactivity of brachial arteries by ultrasound in 20 casino workers exposed to ETS >8 hr/d, 6 d/wk, 9.2 ± 6.1 yr vs. 20 Ctrls	Controls Workers Mean diff	Flow-mediated dilatation (FMD) 10.6 ± 2.3% 6.6 ± 3.4% 4% CI 3-5.4% p < 0.001	Gender and age matched. BP, medical history, BMI, lipid and cholesterol levels (HDL, LDL). Passive smoking strongest predictor of impaired FMD $R^2 = 0.75$, F = 6.1, p = 0.0001
Raitakari *et al*., 1999 Australia	Cross-sectional study of effects of current and past ETS on flow-mediated dilation (FMD) in 3 x 20 adults 15-39 yr	Status: Never Past ETS ETS	FMD (%) 8.9 ± 3.2 5.1 ± 4.1 p < 0.01 2.3 ± 2.1 p < 0.01	ETS exposure decreased FMD (p<0.001). Quitting ETS improved FMD vs current ETS (p<0.01) but still worse than never ETS (p<0.01). Control for bp, dyslipidemia, heart disease, diabetes, age and sex. No gender differences.

Table 8.17a Summary of Cited Studies: Vascular Pathophysiological Effects- Humans.

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Stefanadis *et al*., 1998	Measured aortic distensibility in men during cardiac catheterization for chest pain	Smokers: 16 passive 16 active 16 sham	Decrease in distensibility 21% p<0.001 27% p<0.001 0	5 min smoke exposure caused significant reduction in aortic elasticity in both passive and active smokers vs. sham. Recovery seen in passive group 15 min after cessation.
Sumida *et al*., 1998	Measured diameters of coronary arteries after ACh by angiography in women hospitalized for atypical chest pain. 11 never smokers 8 active smokers 19 ETS exposed	Status: Never Active ETS Never Active ETS	% diameter change Distal LAD 13.7 ± 3.4 p<0.05 -27.2 ± 6.0 p<0.01 -22.3 ± 4.1 p<0.01 Distal LCX 9.7 ± 3.4 p<0.05 -22.4 ± 4.0 p<0.01 -17.3 ± 2.9 p<0.01	ACh caused dilation of distal segments of left descending and left circumflex arteries in never smokers but constriction in ETS and active smokers. In all groups, NTG increased diameter. Suggests active and passive smoke exposure damages endothelium.
Howard *et al.,* 1998 U.S.	Longitudinal study of current, past and passive smokers and change in Initma-Media Thickness (IMT) over 3 yrs. n = 10,914 adults	Smokers: never-ETS never + ETS Past – ETS Past + ETS Current	Progression rate 25.9 ± 2.1 µm/3 yr 31.6 ± 2.0 “ 32.8 ± 2.7 “ 38.8 ± 2.3 “ 43.0 ± 1.9 “	After adjusting for cardiovascular risk factors, lifestyle and demographics, ETS increased progression by 5.9 µm/3yr. No relationship between IMT progression and number of hours exposed.

*Abbreviations: ACh – acetylcholine; AMI – acute myocardial infarction; BMI – body mass index; BP – blood pressure; CFVR – coronary flow velocity reserve; CHD – coronary heart disease; FMD – flow-mediated dilatation; IMT – intima-media thickness; LAD – left anterior descending artery; LCX – left circumflex artery; MI – myocardial infarction; NTG – nitroglycerin; OR – odds ratio; SDNN – standard deviation of normal-to-normal beast interval; SES – socioeconomic status; SHS – secondhand smoke; SS – sidestream smoke

Mack et al. 2003. The effects of ETS exposure on arterial stiffness were evaluated in 227 adult nonsmokers participating in the Vitamin E Atherosclerosis Prevention Study. Intima-media thickness (IMT), and maximum and minimum arterial diameters of the common carotid artery were obtained by B-mode ultrasonography. The percentage change in carotid arterial diameter between maximum and minimum dilation was used to calculate the carotid stiffness index beta. Exposures to passive smoking at home, work, and other sites were ascertained by questionnaire. Home ETS exposures were quantified by number of smokers and number and number of hours

per day of exposure to each smoker's smoking, while exposures at work and other places were recorded as the number of hours of exposure par day. Other measures collected included BMI, total, LDL and HDL cholesterol, total triglycerides, and serum glucose. Subjects exposed to ETS from any source were, on average, significantly older than those not exposed.

Increasing values of age, BMI, IMT, and glucose were significantly associated with increased beta (β), the carotid stiffness index. After adjusting for age, BMI and IMT, the value of β among females increased as the number of ETS sources increased, but not significantly (p for trend = 0.07). There was no evidence of an association in males (p for trend = 0.10). However, when the data were stratified by BMI, β increased with the number of ETS exposures for individuals with BMI >27.1 kg/m^2 (p for trend = 0.048) but not in those with lower BMIs. Similarly, when stratified by age (≥ 55 years), or IMT (≥ 0.707 mm), the trends for increasing β with increasing numbers of ETS sources had P values of 0.09 and 0.05, respectively. In contrast to the analysis by number of ETS sources, the carotid stiffness index was not associated with hours of ETS exposure in either gender. However, after stratification by BMI >27.1 kg/m^2 or IMT ≥ 0.707 mm, there were significant associations between increasing hours of ETS exposure and arterial stiffness (p for each trend = 0.04).

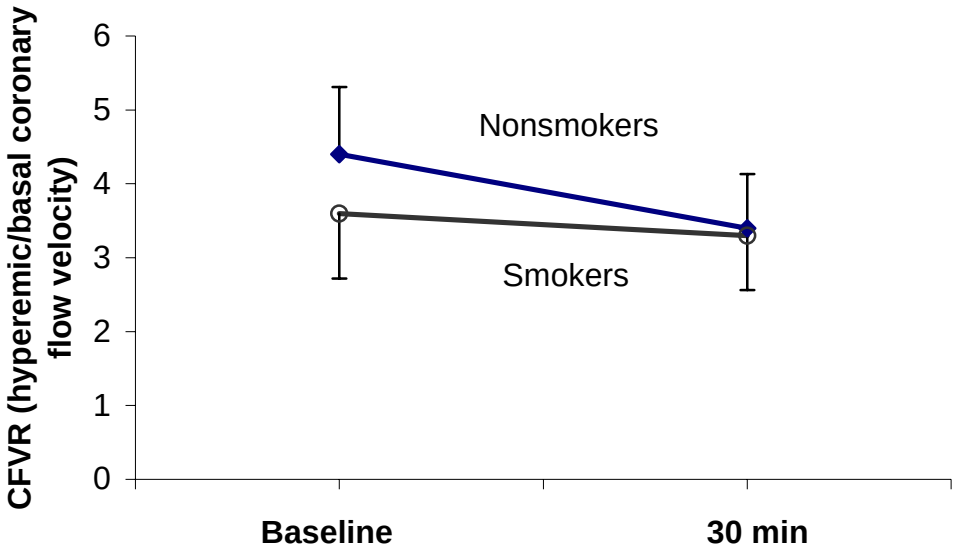
This study was limited by its small size and crude measures of ETS exposure intensity. The results of this study are thus taken to be suggestive that individuals with elevated BMI and IMT values are at greater risk of increased arterial stiffness with chronic ETS exposure. Put another way, individuals with elevated values of BMI and/or IMT have a predisposition to CHD that is exacerbated by ETS exposure.

Otsuka et al., 2001. As a gauge of endothelial function in coronary circulation, coronary flow velocity reserve (CFVR) was measured with transthoracic Doppler echocardiography of the left anterior descending coronary artery. Unlike flow mediated dilatation (see below), which is a measure of endothelial function typically made in brachial arteries, CFVR was based on echocardiographic imaging of coronary arteries to provide an integrated measure of both coronary vascular endothelial function and smooth muscle relaxation. Narrowing of the coronary arteries, or stenosis, was reported by Claeys *et al.* (1996) to be the main determinant of CFVR in patients with myocardial infarction (MI), while Hozumi *et al* (1998) found a CFVR < 2

to be a highly sensitive (92%) and specific (86%) predictor of significant stenosis in the left anterior descending coronary artery. For patients with angina, a CFVR of < 2 was a significant predictor of cardiac events (MI, death, or coronary revascularization) in the year following testing (Chamuleau *et al.*, 2002). Thus decreases in CFVR reflect impaired function in the large epicardial arteries and decreased microcirculation, resulting in a diminished ability of the heart to respond to physiological demands. In the study by Otsuka *et al.*, CFVR was calculated as the ratio of hyperemic velocity (induced by ATP infusion) to basal coronary flow velocity, and reflects the capacity of the arteries to accomodate increased blood flow. Measurements were made in 15 active smoking and 15 nonsmoking males (mean age 27 ± 4 yr) before and after 30 min passive smoke exposure. Smoke exposure occurred in a smoking room with mean CO levels of 6.02 ppm. Carboxyhemoglobin (COHb) levels were measured before and after exposure. During exposure, mean COHb levels (± SD) in nonsmokers rose from 0.40 ± 0.21% to 1.57 ± 0.32%. COHb levels in active smokers before and after exposure were 2.49 ± 1.78% and 2.67 ± 1.79%, respectively. Prior to passive smoke exposure, mean CFVR was significantly higher in non-smokers vs active smokers (4.4 ± 0.91 vs 3.6 ± 0.88, resp., $p = 0.02$), suggesting compromised endothelial function in the latter group. However, after exposure CFVR was not different between nonsmokers and active smokers ($p = 0.83$). This result may, in part, be due to small sample size. Passive smoking significantly reduced CFVR in nonsmokers (4.4 ± 0.91 to 3.4 ± 0.73, $P<0.001$) but not in smokers (3.6 ± 0.91 to 3.3 ± 0.74); in both cases there was no change in heart rate or blood pressure (Fig. 8.03). These data suggest that even a single transient exposure to passive smoke may compromise coronary artery function. No significant differences were seen between groups for age, heart rate, blood pressure, total cholesterol, triglycerides and HDL levels.

The design of the study by Otsuka *et al.* did not allow for an assessment of the long-term effects of passive smoke on CFVR nor a determination of the duration of the effects after exposure cessation. Nevertheless, these results suggest that among healthy young adults, ETS exposure may cause endothelial dysfunction of the coronary circulation, an early step in the development of atherosclerosis.

Figure 8.03 Coronary Flow Velocity Reserve after 30 min ETS



Adapted from Otsuka *et al.*, 2001

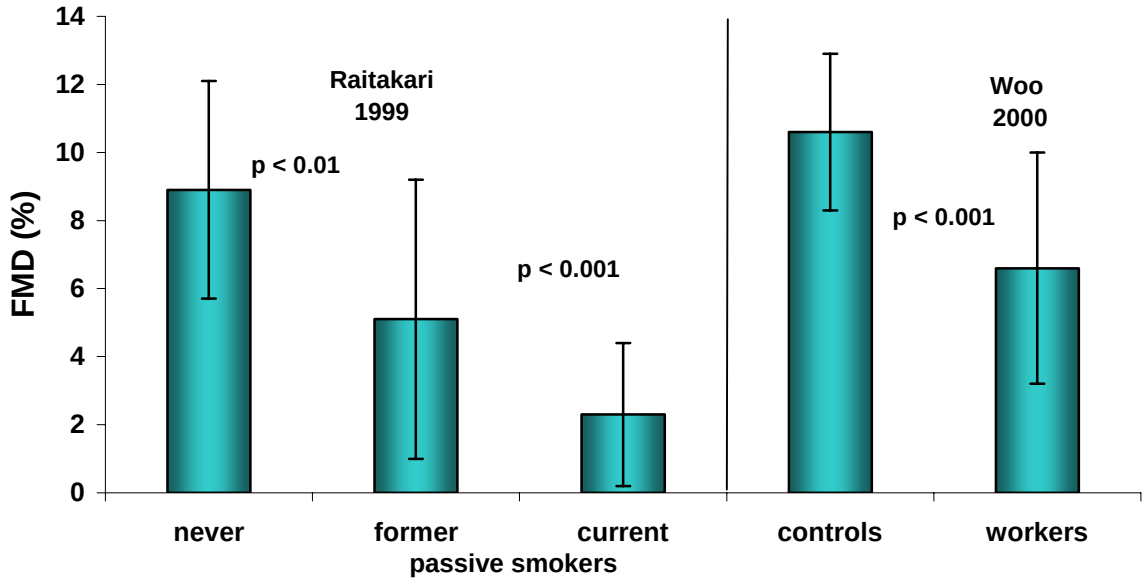
Pope et al., 2001. A characteristic of a healthy cardiovascular system and the associated autonomic nervous system is a high level of heart rate variability (HRV). Measures of decreased HRV have been associated with increased risk of chronic heart failure (Nolan *et al.,* 1998). Pope *et al.* examined changes in both time- and frequency-domain measures of HRV in 16 adults (21-76 yrs) during alternating two-hour periods of exposure to ETS or room air in an airport's smoking and nonsmoking areas. Both areas were monitored for numbers of lit cigarettes, air nicotine, respirable suspended particulates (RSP; > 3μ), and CO. Ambulatory electrocardiograph monitors collected data on all participants during the eight hour experiment for analysis of HRV. Over the eight hour period, nicotine and RSP levels were in the ranges 21-53 $\mu g/m^3$ and 41-166 $\mu g/m^3$, respectively, in the smoking area, and 0-2 $\mu g/m^3$ and 12-43 $\mu g/m^3$, respectively, in the nonsmoking area.

One measure, the standard deviation of normal-to-normal beat intervals (SDNN), correlated most highly with overall measures of HRV and so was used to examine the effect of ETS exposureon HRV. Among six models controlling for various covariates, all ETS exposure variables were negatively and significantly ($p<0.05$) correlated with SDNN. Thus the overall effect of ETS exposure in this study was a decrease in cardiac autonomic function, as measured by HRV, that reversed upon cessation of exposure. This study was small and of short duration so it is not

known whether chronic ETS exposure would result in chronic depression of HRV. However, the acute effects of ETS on HRV could put susceptible individuals at higher risk of a cardiovascular event.

Woo et al., 2000. Flow mediated dilatation (FMD) is an endothelium-dependent response to sheer stress caused by increased blood flow. It is largely mediated by the endothelial release of nitric oxide and prostacyclin which cause the relaxation of the underlying smooth muscle. Since an intact endothelium is required for this response, decreases in FMD reflect decrements in vascular endothelial function and reactivity. In this study, Woo *et al.* evaluated FMD in brachial arteries by ultrasonography in 20 non-smoking casino workers (mean age 36.6 ± 7.0 yr) exposed to ETS for over 8 hr/day, 6 day/wk for 2-24 years (mean 9.2 ± 6.1 yrs). FMD was measured following reactive hyperemia caused by pressure cuff release while endothelium-independent dilatation was measured following nitroglycerin administration. Twenty non-exposed controls were matched for age and gender. Age, gender, active smoking, duration of exposure to ETS, blood pressure, BMI, total serum cholesterol (C), HDL-C, LDL-C, degree of hyperemia and vessel size were included as independent variables in the multivariate analyses. In the nonexposed controls, FMD was 10.6 ± 2.3% compared to 6.6 ± 3.4% in passive smokers (mean difference 4%; 95% CI 3-5.4%; $p<0.001$) (Fig. 8.04). In contrast, nitroglycerin-induced responses were similar in the two groups suggesting that the dysfunction was at the level of the endothelium. Passive smoke exposure was thus associated with impaired FMD which in turn has been related to the extent of coronary disease (1-, 2- or 3-vessel disease) in both CHD and non-CHD patients (Neunteufl *et al.,* 1997). No effect of duration of passive smoking on FMD was seen ($p=0.63$), however the heavy exposure to ETS, >8 hr/d for over 2 years, may have resulted in a maximal response which would mask a dose-response relationship. After multivariate analysis, passive smoking was the strongest predictor of impaired FMD ($ß = -0.59$, $p = 0.0001$), independent of age, gender and other measured variables (model $R^2 = 0.75$; F value = 6.1, $p = 0.0001$).

Figure 8.04 Impairment of Flow-Mediated Dilatation with ETS Exposure



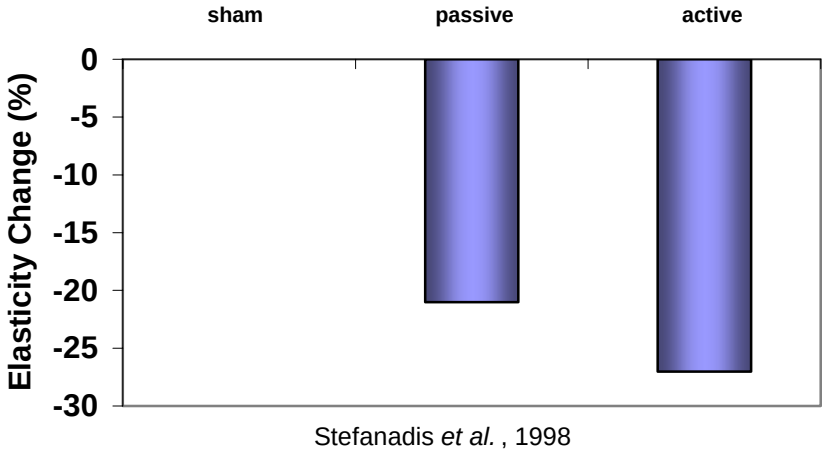
Raitakari et al., 1999. The effects of ETS exposure on vascular reactivity and the potential for recovery following exposure cessation were studied in this cross-sectional study. Reactive hyperemia was induced by pressure cuff release, and endothelium-dependent flow-mediated dilatation (FMD) and endothelium-independent (nitroglycerin-induced) dilatation were measured by ultrasonography. The study included 60 young adults (age 15-39 yrs): 20 with no exposure to active or passive smoking (controls), 20 nonsmokers with passive smoke exposure for ≥ 1 hr/d, for ≥ 2 yr, and 20 former passive smokers. Smoke exposure was self-assessed by questionnaire with recent exposure verified by measurement of salivary cotinine. The study controlled for age, sex, dyslipidemia, blood pressure, diabetes, and history of heart disease. Among never smokers, the mean (± SD) FMD was 8.9 ± 3.2%. In former passive-smokers this value was 5.1 ± 4.1%, which dropped to 2.3 ± 2.1% ($p<0.001$) in current passive-smokers (Fig. 8.04). After administration of nitroglycerin, no significant difference was seen among groups for endothelium-independent dilatation. There were also no significant gender differences. In the former passive-smoking group, FMD was most impaired in recent quitters (< 2 yrs; FMD 1.2 ± 1.7%) versus those quitting more than two years previously (FMD 5.8 ± 4.0%; $p \leq 0.05$). Thus ETS exposure was seen to significantly impair vascular responsiveness as measured by FMD and, consistent with other studies, the tissue most adversely affected by ETS exposure was the vascular endothelium. These effects appeared to be at least partially reversible following

cessation of smoke exposure. Although limited by its small size and cross-sectional nature, the inverse relationship between ETS exposure and FMD is consistent with a causal role of ETS in CHD.

Stefanadis et al., 1998. Loss of arterial flexibility is associated with increased risk of CHD. Stefanadis *et al* studied the association between passive smoking and the elastic properties of the aorta via measurement of instantaneous diameters and pressures in the descending thoracic aorta during and after active, sham and passive smoking. All participants in this study were males (mean 48 ± 10 yr) undergoing diagnostic cardiac catheterization for evaluation of chest pain. The study included 16 nonsmokers (for passive smoke exposure) and 32 current, long-term smokers (≥ 1 pack/d, ≥ 1 yr). For this study the latter group was divided into 16 active, and16 sham smokers. Passive smokers were exposed to ETS in an exposure chamber with CO levels of 30 ppm for 5 min. Active smokers smoked one filtered cigarette (1 mg nicotine) in 5 min while sham smokers "smoked" one unlighted cigarette for 5 min. Arterial measurements were made at baseline and 1, 2, 3, 4, 5, 10, 15 and 20 min after the start of smoke exposure. Aortic distensibility, which measures vessel diameter as a function of vessel pressure, was used as a gauge of aortic elasticity. Large distensibility values represent healthy aortic elasticity while low values indicate deteriorated properties. In this context both passive and active smoking caused decrements in aortic distensibility. Whereas sham smoking did not change distensibility, passive smoking caused a significant 21% decrease from 2.02×10^{-6} to 1.59×10^{-6} cm^2/dyne during the 5 minutes of passive smoke exposure ($p<0.001$) with gradual recovery over the subsequent 15 min to near sham values. Active smoking decreased mean distensibility 27% (from 2.08 to 1.51×10^{-6} cm^2/dyne), and did so more rapidly than did passive smoking, with no recovery during the subsequent 15 min (compared to sham, $p<0.001$) (Fig. 8.05). This study suggests that both active and passive smoking can cause acute deterioration of elastic properties of the aorta and thereby compromise aortic function.

All participants in this study were men, most of whom had CHD, which limits the generalizability of these results. It is unknown whether women, those without CHD, or (since the aorta loses elasticity with age) younger individuals would respond in the same way. However, these data suggest that people with CHD may be especially at risk from ETS exposure.

Figure 8.05 Loss of Aortic Elasticity with Active and Passive Smoking.



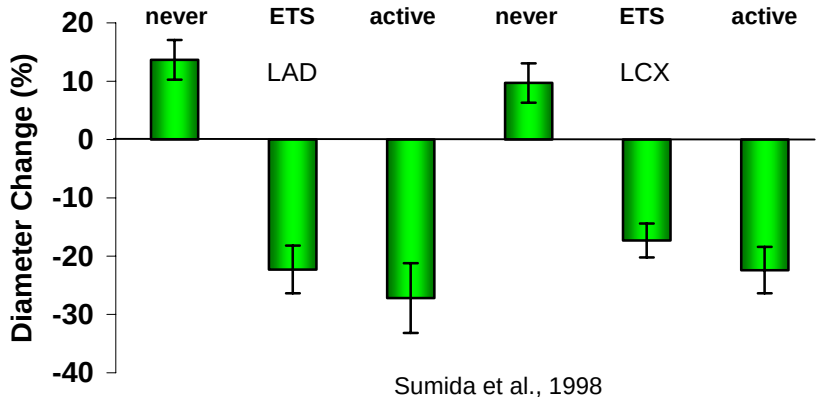
Stefanadis *et al.* , 1998

Sumida et al. (1998) used quantitative coronary angiography to measure diameters of the epicardial coronary artery in response to intracoronary injection of acetylcholine (ACh). The subjects of this study were 38 women admitted to a hospital in Japan for diagnostic cardiac catheterization for evaluation of atypical chest pain. Included were 11 never-smokers not exposed to ETS, 19 passive smokers, and 8 active smokers, all of similar age. The passive smoking group included life-long nonsmokers with a self-reported history of exposure to ETS at home, work or both for ≥ 1 hr/day for ≥ 10 years. Active smokers were those who smoked ≥ 20 cigarettes per day for > 10 years. Urinary cotinine levels, measured at hospital admission, were not detectable in nonsmokers not exposed to ETS (<5.0 ng/ml). These levels were 9.1 ± 0.5 ng/ml in passive smokers, and 1,350 ± 60 ng/ml in active smokers. All patients were reportedly free of important coronary risk factors, and there were no significant differences among groups with respect to age, blood pressure, total cholesterol, LDL-C and HDL-C.

Lumen diameters were measured at the proximal, middle and distal segments of the left anterior descending (LAD) and the left circumflex (LCx) coronary arteries by computer-assisted angiography at baseline and after administration of acetylcholine (ACh) and nitroglycerin (NTG). The reponse to treatment was expressed as the percent change in coronary diameter from baseline. In the nonsmokers, ACh significantly dilated the distal segment of the LAD but not the proximal and middle segments. In the LCx, ACh significantly dilated the middle and distal but not the proximal segments. By contrast, in the passive smokers, ACh significantly constricted all segments of the left coronary artery (Fig. 8.06). The degree of constriction in

passive smokers was similar to that seen in active smokers. No significant differences were found in ACh-induced constriction between those with light passive smoke exposure (3.7 ± 1.4 hr/day) versus heavy (7.8 ± 2.6 hr/day). There were also no significant differences in response to NTG among active, passive and nonsmokers.

Figure 8.06 Smoke Exposure and Modified Arterial Response to Acetylcholine

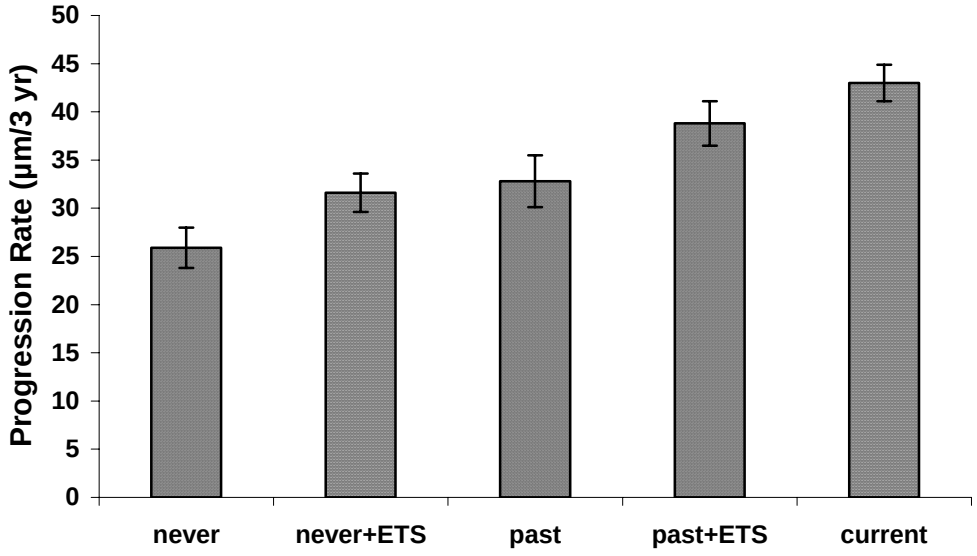


In the absence of underlying disease, vasodilation is the normal arterial respose to ACh. This effect is mediated by the endothelium mainly through the release of nitric oxide (NO). On the other hand, ACh causes vascular smooth muscle to constrict. Thus the arterial response to ACh is a result of the balance between the dilator action of endothelium-derived substances, including nitric oxide, and a direct constrictor action of ACh on smooth muscle. The constriction of all segments of the coronary arteries in response to ACh among the patients exposed to smoke, either passively or actively, sharply contrasts with the dilatory response seen in nonsmokers and suggests that the coronary endothelium may have been damaged by smoke exposure. Endothelial damage is further supported by the similarity among all exposure groups to the dilatory effects of NTG, a non-endothelium-dependent response. However, the subjects were admitted to a hospital because of chest pains, so it is possible that undetected pre-existing conditions other than smoke exposure may have distinguished the smokers from nonsmokers. This study found no significant differences in arterial diameter changes between light and heavy ETS exposure. Although the small study size precludes a definitive conclusion regarding the

exposure-response relationship, these results suggest that the observed effects of ETS on arterial dilatation may saturate at a relatively low exposure level.

Howard et al. (1998) used data from the Atherosclerosis Risk in Communities Study (ARIC) in a longitudinal assessment of the effects of active and passive smoking on the progression of atherosclerosis over three years. This population based study included 10,914 middle-aged adults (avg age 54 yr). The intima-media thickness (IMT) of carotid arteries was measured by ultrasound at baseline and three years later. Smoking history and ETS exposure were self-assessed by questionnaire. Covariates included blood pressure, LDL-cholesterol, diabetes, fat intake, leisure time activity, education, alcohol use, and BMI. The group was divided into 2,956 current smokers, 1,849 past-smokers with ETS exposure (past+ETS), 1,344 past-smokers without ETS exposure (past–ETS), 2,449 never-smokers with ETS (never+ETS), and 2,316 never-smokers with no ETS exposure (never–ETS).

Figure 8.07 Progression of Arterial Intima Media Thickness with Smoke Exposure



Howard *et al.* , 1998

Using smoking category as the primary independent variable, there was a significant progressive increase in wall thickness from never smokers (never-ETS), through those exposed to ETS, to current smokers (Fig. 8.07). In the model with all adjustments, ETS increased progression by 5.9

μm over three years (p = 0.01). Current smoking versus never-exposed increased progression by 17.1 μm/3 yrs (43-25.9=17.1), 34.5% (5.9 μm/17.1) of which was attributable to ETS exposure.

8.1.5. Vascular Pathophysiological Effects – Experimental Animals

Table 8.17b Summary of Cited Studies: Vascular Pathophysiological Effects - Experimental Animals

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Knight-Lozano *et al*., 2002	Laboratory exposure of atherosclerosis-prone mice to SHS. Mitochondrial damage and lesions measured in aorta.	$ApoE^{-/-}$ mice 30 mg/m^3 21d " 42d Mitochondrial lesions 1 mg/m^3 42d 30 mg/m^3 42d	Aortic lesion area +76% vs no SHS +156% " Lesions/16 kilo-bases 1.3 6.0 p<0.001	Significant increase in aorta lesion area (p<0.05), and in mitochondrial DNA damage after SHS exposure. Hypercholesterolemia increased SHS damage to mitochondria and aorta wall.
Gairola *et al*., 2001	Laboratory exposure of atherosclerosis-prone mice to side stream smoke (SS). Lesions and lipids measured in aorta.	 SS Control SS Control	Lesion area 33 ± 11% 10 ± 8% Cholesterol 7 wk 718 ± 61 mg/dl 553 ± 26 mg/dl	Significant increase in area of aorta covered by lesion after SS exposure (p<0.001). Transient increase in plasma cholesterol at 7 wks in SS mice but back to control levels by 14 wks.

Knight-Lozano et al., 2002. $ApoE^{-/-}$ mice lack apolipoprotein E, a high-affinity ligand for lipoprotein receptors, and as a result have elevated levels of serum LDL-C and triglycerides, and develop atherosclerotic plaques in a manner similar to humans. $ApoE^{-/-}$ mice and the normocholesterolemic mouse strain, C57BL/6, were compared in this study of the effects of hypercholesterolemia and smoke exposure on atherosclerotic lesion formation and mitochondrial damage in cardiovascular tissue. Mice were exposed to second hand smoke (SHS; a surrogate for ETS) at 1 and 30 mg/m^3 total suspended particulates (TSP) or filtered air 6 hr/d, 5 d/wk for 42 days, or to air for 21 days followed by 21 days of SHS. Examination of the aortas of SHS-exposed (30 mg/m^3) compared to non-exposed $ApoE^{-/-}$ mice revealed a mean increase in lesion size of 76% at 21 days and 156% at 42 days. In contrast, no lesions were observed in the aortic sinus region of C57BL/6 mice in any exposure group. However, comparison of lipid staining

with oil red O (which is used to visualize atherosclerotic lesions) in entire aortas from SHS-exposed vs non-exposed mice revealed a 4.5-fold increase in stained area for $ApoE^{-/-}$ mice ($p<0.05$), and 2.1- and 3.7-fold increases for C57BL/6 mice at 21 and 42 days respectively.

Quantitative polymerase chain reaction was used to assess damage to aortic mitochondrial DNA. At both high (30 mg/m^3) and low (1 mg/m^3) TSP, significant mitochondrial damage was observed for both mouse strains. This effect was more pronounced in the $ApoE^{-/-}$ than the C57BL/6 mice, suggesting an interaction between hypercholesterolemia and SHS exposure ($p<0.001$). While higher or longer exposures caused substantially more mitochondrial damage ($p<0.001$), even the more environmentally relevant dose (1 mg/m^3) resulted in statistically significant damage ($p<0.001$). Mitochondrial damage could affect cardiovascular cell function through the increased formation of reactive nitrogen and oxygen species. These radicals can in turn oxidize LDL, which enhances its uptake into atherosclerotic plaques, and damage mitochondrial proteins, thereby disrupting energy production and intracellular signaling. These results are consistent with the view that oxidative stress mediates the link between ETS and cardiovascular disease.

Gairola et al., 2001. As described above, $ApoE^{-/-}$ mice develop atherosclerotic lesions very similar to those seen in human disease, including the formation of fatty streaks and fibrolipid lesions. In this study, female $ApoE^{-/-}$ mice (8-9 wks old) were fed a modified diet containing 21% w/w saturated fat and 0.15% w/w cholesterol, and then divided into control and sidestream smoke (SS) exposed groups. Animals were exposed to SS at 25 mg/m^3 particulates for 6 h/d, 5d/wk for 7, 10 or 14 weeks. Upon sacrifice the intimal surfaces along the arch, thoracic and abdominal sections of the aortas were examined microscopically for lesions. The lipid content of aortic tissues was also measured. Atherosclerotic lesions covered greater areas in SS-exposed mice compared to controls starting at the earliest time (7 weeks) with a significantly more rapid increase in size through 14 weeks. This was especially pronounced in the thoracic region of the aorta, which is not normally a lesion-susceptible area. In SS-exposed animals, 33 ± 11% of the intima was covered by lesions versus 10 ± 8% in controls ($P<0.001$). The lesions were also thicker in the SS mice as verified by an increase in esterified and unesterified cholesterol in these tissues. Macrophages were the predominant cellular component of the lesions. Exposure to SS was also associated with a modest, but statistically significant, transient increase in plasma

cholesterol levels at 7 weeks (SS, 718 ± 61 vs Ctrl, 553 ± 26 mg/dl; p=0.027) that was not evident at the later time points. This transient increase may have been related to the increase in atherosclerosis in the SS-exposed group.

There are differences between the exposure conditions in this study and realistic human ETS exposures. The mice were exposed to levels of smoke constituents roughly ten times the respirable particulates in a smoky bar (Anderson *et al.,* 1991). However, the most prolonged exposure was for only approximately 10% of their normal life span: the dose-time integrals for the lower exposure groups may thus be relatively realistic. Although the cardiovascular consequences of briefer but more intensive ETS exposure may differ from those associated with chronic lower level exposure, in this animal model ETS exposure was clearly associated with promotion of atherosclerosis.

8.1.6. Hematological Effects

Table 8.28 Summary of Cited Studies: Hematological Effects

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Moffatt *et al.,* 2004	Measured HDL and total cholesterol before and after 6 hr ETS. 12 male nonsmokers.	6 hr ETS Post ETS 8 hr 16 hr 24 hr Post ETS 8 hr 16 hr 24 hr	HDLC decrease 37% 31% 28% Total:HDLC pre- vs post ETS 4.1 vs 4.9 4.2 vs 5.0 4.2 vs 4.9	Single, long-duration ETS exposure lowered HDLC in healthy adult males for over 24 hours post-exposure.
Moskowitz *et al*., 1999	Cross-sectional study of CHD risk factors in pubertal children vs ETS, race, sex in 408 twin pairs 11-15 yr	Family ETS exposure ETS No ETS ETS No ETS ETS + family history CHD No CHD	Level (mmol/ml) HDLC 1.19 ± 0.22 1.26 ± 0.28 $HDLC_2$ 0.30 ± 0.16 0.35 ± 0.20 HDLC 1.18 ± 0.23 1.25 ± 0.23	Lower levels of HDL-C and subfraction 2 (HDL_2-C) in kids from smoking families ($p \leq 0.01$, $p \leq 0.001$, resp). Even lower HDL-C in smoking families with CHD history ($p<0.001$).

Reference Area	Study description	Exposure to smoke	Outcome and RR, OR (95% CI)	Comments*
Valkonen & Kuusi, 1998	Measured HDL-C, and antioxidants before and after ETS	30 min ETS Post ETS 6 hr	Blood changes Vit C -25% SH -21% Oxidized LDL	30 min ETS exposure lowered blood antioxidant capacity up to 6 hr post-exposure.

Moffatt et al., 2004. Active smoking has been associated with a decrease in plasma high-density lipoprotein cholesterol (HDL-C). To address whether ETS has similar effects, Moffat *et al*. examined the effects of 6 hours of exposure to ETS on blood levels of HDL-C and its subfractions, HDL_2-C and HDL_3-C, in 12 male non-smokers. Subjects were 21-31 years of age and reportedly free from diseases known to alter lipid profiles. During the first of three consecutive days, baseline data were collected prior to ETS exposure. At 6 am, 2 pm and 10 pm, respiratory carbon monoxide (CO) and HDL-C levels were determined. ETS exposure occurred on the second day for 6 continuous hours during which levels of CO and nicotine were monitored to maintain levels comparable to establishments in which smoking was permitted (12 ppm and 16.0 $\mu g/m^3$, respectively). Respiratory CO levels and blood samples were again taken at 8, 16, and 24 hours post ETS exposure. Dietary records were obtained for the three days prior to, during, and following exposure.

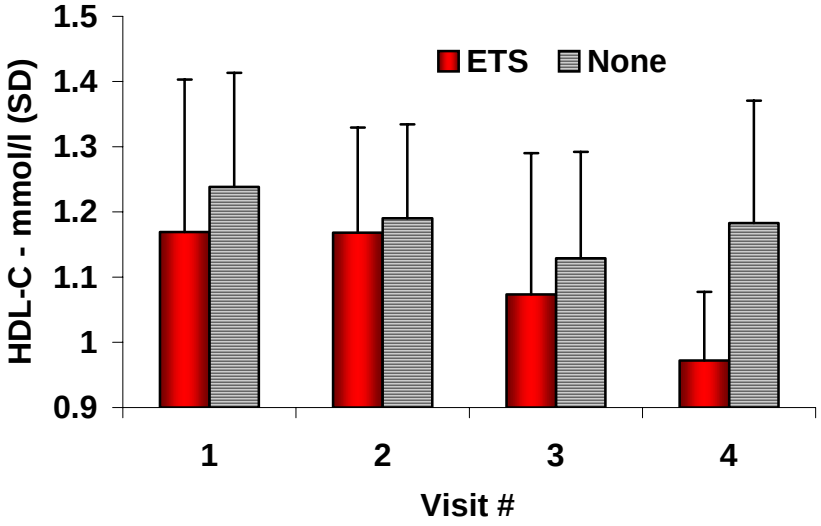
HDL-C levels were significantly reduced at 8 hrs (18%), 16 hrs (14%), and 24 hrs (13%) post-ETS exposure. Similarly, following ETS exposure, the subfraction HDL_2-C was also significantly reduced: 8 hrs (37%), 16 hrs (31%), and 24 hrs (28%). By contrast, total cholesterol levels were not different between pre- and post-ETS exposures. As a result, the ratio between total cholesterol and HDL-C significantly increased following exposure: 8 hrs (4.9 vs 4.1), 16 hrs (5.0 vs 4.2), 24 hrs (4.9 vs 4.2). The ratio between HDL_2-C and HDL_3-C decreased between pre- and post-ETS exposure: 8 hrs (0.31 vs 0.45), 16 hrs (0.36 vs 0.53), 24 hrs (0.36 vs 0.48). Pre- and post-exposure respiratory CO levels were not different, but during exposure CO increased from 3.61 ± 0.21 to 7.31 ± 0.51 ppm.

This study was small and the ETS exposure of long duration. How the results apply to individuals with shorter and/or more frequent exposures to ETS is not known. However, the study did find that a single ETS exposure of long duration significantly altered the plasma lipid profiles in healthy males, and that these changes required more than 24 hours to reverse

following cessation of ETS exposure. The depression of HDL-C, but not total cholesterol levels, following exposure suggests a mechanism by which ETS exposure may promote atherosclerosis.

Moskowitz et al,. 1999. Most investigations of the association between CHD and ETS focus on adults. In this study, Moskowitz *et al.* examined how CHD risk factors, passive smoking, gender and race are related in pubertal children. Data were collected during four visits at 18-month intervals from 113 twin pairs from 11-15.5 years of age. Information on family and health histories, smoking, alcohol use, blood pressure, and anthropometrics was collected by questionnaire and during interview. Biochemical assays provided data on blood HDL-cholesterol (HDL-C), LDL-C, and cotinine. HDL-C subfraction 2 (HDL_2-C) was also assessed as most of the variation in HDL-C is due to this subfraction and others have shown that CHD deaths occur more frequently in families with low levels of HDL_2-C (Bodurtha *et al.,* 1987). At the first visit, children with long-term passive smoke exposure had significantly lower HDL-C (visit 1: 1.19 ± 0.22 vs 1.26 ± 0.28 mmol/L; $p \leq 0.01$) and HDL_2-C (0.30 ± 0.16 vs 0.35 ± 0.20 mmol/L, $p \leq 0.01$) than kids from nonsmoking families. In addition, over the course of the four visits, HDL-C significantly decreased among children exposed to ETS compared to children in nonsmoking families ($p \leq 0.001$ for trend; Fig 8.08). The negative effects of passive smoke exposure on HDL-C levels were more pronounced in children of families with a history of cardiac disease versus those without (visit 1: 1.18 ± 0.23 vs 1.25 ± 0.23 mmol/mL; visit 4: 0.98 ± 0.10 vs 1.19 ± 0.18 mmol/mL; $p<0.001$). This study indicated that in children also, ETS exposure has a deleterious effect on HDL-C levels, a risk factor for CHD. In addition there appeared to be differences in susceptibility to ETS effects related to race, gender and familial history of cardiac disease.

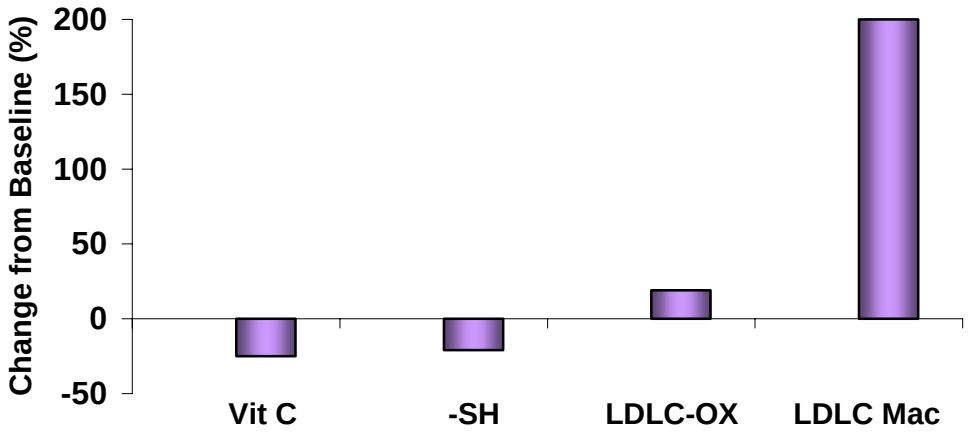
Figure 8.08 ETS Exposure and HDL-C Levels in Children



Adapted from: Moskowitz *et al.*, 1999

Valkonen and Kuusi (1998) examined the blood of nonsmokers prior to, and 1.5 and 6 hours after starting a 30-min exposure to ETS. They measured serum cholesterol, HDL-C, triglycerides and LDL-C levels, lipid- and aqueous-soluble antioxidants, and the combined ability of all antioxidants to resist artificially induced LDL-C peroxidation. Acute exposure to ETS resulted in a 25% decrease in serum ascorbic acid starting at 1.5 hrs after exposure and lasting 6 hrs ($P<0.001$), and a gradual decrease in sulfhydryls by 21% from baseline by 6 hrs ($P<0.063$) signifying a loss of antioxidant defenses. There was a concomitant 19% decrease in the resistance of LDL-C to Cu^{2+}-initiated oxidation. Uptake by cultured macrophages of LDL-C isolated following ETS exposure was found to be 1.6-2.3 times higher than that of unexposed LDL-C (Fig 8.09). Thus, ETS exposure enhanced peroxidation of LDL-C and its accumulation in macrophages, both of which occur during the formation of atherosclerotic plaques. In a subsequent study, peroxidation of LDL-C after ETS exposure was ameliorated by ascorbic acid administration (Valkonen & Kuusi, 2000), consistent with the role of peroxidation in plaque formation.

Figure 8.09 Effect of ETS Exposure on Blood Anti-oxidants, Lipid Oxidation and Accumulation in Macrophages



fr. Valkonen and Kuusi, 1998

Vit C – ascorbic acid; -SH – protein sulfhydryls; LDL-OX – oxidized LDL

8.2. Other Pathophysiological Evidence

The 1997 report described evidence for pathophysiological mechanisms that may mediate the cardiovascular effects of ETS. Additional pathophysiological evidence is reviewed below.

8.2.1. Internal Carotid Artery Thickness (IMT)

Results from the British Regional Heart Study (Ebrahim *et al.,* 1999) suggest that IMT of the common carotid artery is strongly associated with risk factors for stroke while IMT of the bifurcation was more directly associated with plaque and ischemic heart disease. It appeared that the presence of plaques rather than IMT *per se* was the more important predictor of disease risk. The presence of plaques was in turn significantly associated with increasing levels of fibrinogen in men ($P<0.01$ for trend), and to a lesser extent in women. ETS exposure was not evaluated in this study, however, Iso *et al.* (1996) found an association between fibrinogen levels and ETS exposure in women (see below).

The studies by Chambless *et al*. (1997. 2000) were not specifically designed to examine the effects of smoke exposure on vascular disease; however, these studies are included here as they substantiate the importance of arterial wall thickness as a risk factor for cardiovascular disease.

Thickening of arterial walls is associated with increased risk of CHD, stroke and death (Bots *et al.,* 1999).

Chambless et al. (1997) related the mean carotid intima-media thickness (IMT), measured by ultrasonography, to CHD incidence during a 4-7 year follow-up among 7,289 women and 5,552 men (45-64 yr). CHD incidents included myocardial infarction (MI), CHD death, and probable CHD. Hazard rate ratios (HRR) were calculated for incident CHD as a function of IMT. After adjusting for age, race, diabetes, cholesterol (C), LDL-C, HDL-C, blood pressure, smoking (pack-years), and alcohol use, an increase in IMT of 0.19 mm (≈ 1 SD) was associated with a HRR for CHD of 1.42 (95% CI 1.24-1.64) in women and 1.18 (95% CI 1.06-1.32) in men. In women, current vs ever smoking had an associated HRR of 3.64 (95% CI 2.30-5.76) while in men this HRR was 2.27 (95% CI 1.53-3.35). Smoking cessation was associated with dramatically decreased HRRs. In female ex-smokers versus never smokers, the HRR was 1.20 (95% CI 0.64-2.27), and the similar comparison for men gave a HRR of 1.17 (95% CI 0.79-1.73). Interestingly, the risk for CHD with increasing IMT increased more rapidly at low IMT values than at higher IMT suggesting a higher sensitivity to smoke in arteries with smaller IMTs at baseline.

The prospective nature of this study made it possible to link IMT measured at baseline with subsequent CHD, and so directly examine the risk of CHD incidents as a function of IMT. A limitation of this study was the basing of mean IMTs on a single assessment. Incomplete sets of ultrasound data necessitated exclusion of some participants and imputation of some IMT measurements for most others using maximum likelihood techniques. This study controlled for most major CHD risk factors; however, diet and socioeconomic status were not included. While this study was not designed to specifically examine the effects of smoke exposure on IMT, active smoking was seen to increase the risk of CHD, a relationship that is already well known. The association between IMT and CHD incidence is important in the context of increases in IMT associated with passive smoke exposure reported in other studies (see Howard *et al.*, 1998).

Chambless et al. (2000) conducted a prospective study of ischemic stroke. The mean carotid intima-media thickness (IMT) was measured by ultrasonography and was related to stroke incidence during a 6-9 year follow-up among 7,865 women and 6,349 men (45-64 yr). Hazard

rate ratios (HRR) were calculated for incident ischemic stroke as a function of IMT relative to the reference category of 0.6 mm. The HRRs for mean IMT ≥ 1 mm compared to ≤ 0.6 mm were 8.5 for women (95% CI 3.5-20.7) and 3.6 for men (95% CI 1.5-9.2). A graded increase in the event rate or hazard rate ratio was seen in both men and women. After adjusting for HDL-C, LDL-C, smoking, hypertension, body mass index (BMI), sports activity, diabetes, fibrinogen levels, left ventricular hypertrophy and white blood count, at low IMT, a 0.18 mm increase in IMT gave a HRR for stroke of 1.21 (95% CI 1.05-1.39) in men and 1.36 (95% CI 1.16-1.59) in women. These results suggest that mean IMT is predictive for subsequent ischemic stroke. As in the study on CHD, the stroke risk reflected in the HRR increased more rapidly at low IMT than at higher IMT. It should be noted that although increased carotid wall thickness played a role in the etiology of stroke, the thickening of the carotid wall as measured in this study was not assumed to be the sole cause of ischemic stroke. Rather it was a surrogate marker for the existence of etiologically significant lesions elsewhere. Whereas CHD is due almost exclusively to atherosclerosis, stroke has a mixed etiology that includes degeneration of intracerebral arteries as well as atherosclerosis of the carotid and basilar arteries, and the large arteries of the brain.

This study shares the limitations reported above for the ARIC CHD study, including basing of IMTs on single assessments, incomplete sets of ultrasound data requiring imputation of some IMT measurements and no control for some potential confounders such as diet and socioeconomic status. As with the report above, the effects of smoke exposure on IMT were not addressed; however, these results complement the longitudinal study by Howard *et al* (1998) that specifically looks at passive smoking in the context of the ARIC IMT data.

8.2.2. Endothelial Function

Several recent studies in humans and animals continue to document that ETS exposure damages vascular endothelium. This is usually manifested as impaired endothelium-dependent dilatation of coronary arteries. Woo *et al.* (2000) found significantly ($p<0.001$) diminished flow-mediated dilatation (FMD) in casino workers extensively exposed to ETS compared to unexposed controls. FMD was also observed by Raitakari *et al* (1999) to be significantly reduced in former passive ($P<0.01$) and current passive ($P<0.001$) smokers compared with unexposed nonsmokers. In a study by Sumida *et al.* (1998), acetylcholine (ACh) induced coronary artery dilatation in nonsmoking women but caused significant arterial constriction in women passively or actively

exposed to smoke ($p<0.01$). Yet another measure of endothelial function, coronary flow velocity reserve, was found by Otsuka *et al.* (2001) to be significantly diminished ($p<0.001$) in young men following a 30 min exposure to passive smoke. In studies of atherogenesis in rabbits, secondhand smoke increased intimal lesion size in the aorta and inhibited ACh-induced relaxation of isolated aortic rings (Hutchison *et al.,* 1999). This effect may be mediated by ETS's ability to inhibit nitric oxide synthase and decrease endothelial arginine (Hutchison *et al.,* 2001). In both the human and animal studies, similar aortic responses in exposed and unexposed groups to endothelium-independent (nitroglycerin-induced) dilatation indicated that the endothelium is adversely affected by ETS exposure.

8.2.3. Exercise Tolerance

The deleterious effects of exposure to smoke and CO on oxygen transport and usage during exercise were recently reviewed by McDonough and Moffat (1999), but no data beyond those included in the 1997 report were identified by OEHHA staff. The OEHHA (1997) report found suggestive evidence that ETS exposure impairs exercise tolerance, especially in patients with existing CHD but also to a lesser extent in healthy individuals..

8.2.4. Lipid Profile

The growth of atherosclerotic plaques is associated with the accumulation of LDL-cholesterol (LDL-C) by macrophages, the precursors to foam cells in atherosclerotic lesions. Peroxidation of LDL-C also enhances its penetration of the arterial intima, binding to the extracellular matrix of intimal cells (Wang *et al.,* 2001), and uptake by macrophages. Valkonen and Kuusi (1998) documented the loss of antioxidants as well as a decreased resistence of LDL-C to oxidation in the blood of nonsmokers exposed to ETS. In addition, the uptake of LDL-C from ETS-exposed subjects by cultured macrophages was substantially enhanced. Thus, ETS exposure enhanced peroxidation of LDL-C and its accumulation in macrophages, both of which occur during the formation of atherosclerotic plaques. In a subsequent study, peroxidation of LDL-C after ETS exposure was ameliorated by ascorbic acid administration (Valkonen & Kuusi, 2000), consistent with the role of peroxidation in plaque formation.

Whereas LDL-C promotes atherogenesis, HDL-C is protective and low HDL-C levels are considered a risk factor for CHD. In the study by Moskowitz *et al.* (1999), HDL-C levels in

children with long-term passive smoke exposure were lower than in children from nonsmoking families (1.21 ± 0.26 vs 1.31 ± 0.26 mmol/L; $p \leq 0.01$). This difference was especially pronounced for the subfraction HDL_2-C (0.31 ± 0.18 vs 0.41± 0.19 mmol/L, trend $p \leq 0.001$). This subfraction accounts for most of the variation in HDL-C and, in families with low levels of HDL_2-C, is associated with more frequent CHD death (Bodurtha *et al.,* 1987). Decreases in HDL-C and its subfractions were also observed in adults after ETS by Moffatt et al. (2004).

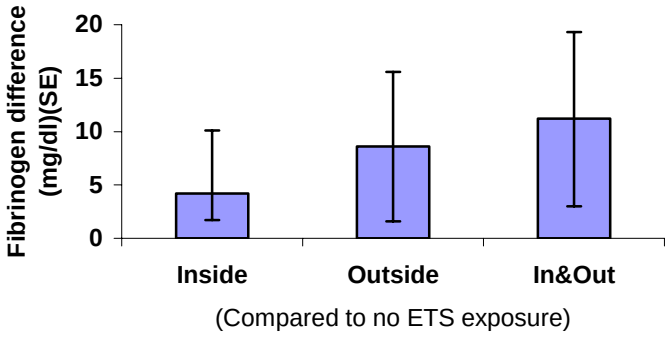
8.2.5. Platelet Aggregation and Endothelial Damage

Activation of platelets is associated with damage to the lining of coronary arteries, and with the synthesis and secretion of thromboxanes, which in turn promote vasoconstriction and platelet aggregation. Levels of thromboxane in the blood are thus a measure of platelet activation and signal an increased likelihood of thrombus formation. The formation of thrombi may elevate the risk of an ischemic event such as myocardial infarction. Schmid *et al.* (1996) examined malondialdehyde (MDA), plasma and serum thromboxane B_2 (TXB_2), 11-dehydrothromboxane B_2, and conversion of exogenous arachidonic acid to TXB_2 and to hydroxy-5,8,10-heptadecatrienoic acid in 12 active smokers and 12 nonsmokers following exposure to ETS. For both groups, both single 60-min exposures and exposures repeated on 5 successive days resulted in significant increases ($p<0.05$) in all parameters except serum TXB_2. Whereas prior to acute smoke exposure, the levels of all six compounds were significantly lower ($p<0.5$) in nonsmokers than in smokers, after 4 days of ETS exposures, the MDA and serum TXB_2 levels in nonsmokers rose and became similar to those of active smokers. Among nonsmokers, levels of MDA and plasma TXB_2 remained elevated 6 hours after exposure. Thus the acute effects of ETS on platelet activation were more pronounced in nonsmokers than in smokers, possibly due to chronic activation of platelets in the latter group, and repeated ETS exposure making nonsmokers more like smokers in this respect. The effect was also observed in studies by Sinzinger and Kefalides (1982) and Burghuber *et al.* (1986). These studies, described in Cal/EPA (1997), document a significant decrease in platelet sensitivity to the antiaggregatory effects of PGI_2 among nonsmokers but not active smokers following acute smoke exposure.

8.2.6. Fibrinogen Levels

Elevated plasma fibrinogen is an important coronary risk factor associated with both active and passive smoking. In a cross-sectional study of 1,780 Japanese women, Iso *et al.* (1996) reported that in women exposed to ETS outside the home, fibrinogen levels were 8.6 (95% CI 1.6-15.6) mg/dl higher than among non-exposed women. For ETS exposure in the home only, fibrinogen levels were 4.2 mg/dl (95% CI 1.7-10.1) higher, while in women exposed both in and outside the home, fibrinogen levels were 11.2 (95% CI 3.0-19.3) mg/dl higher than in non-exposed women (Fig. 8.10).

Figure 8.10 Increased Plasma Fibrinogen in Women Exposed to ETS Inside and/or Outside the Home



Adapted from Iso *et al.*, 1996

8.2.7. In vitro Studies

Wong et al., 2004. This study examined the responses of fibroblasts exposed to solutions containing whole sidestream smoke or whole mainstream smoke in vitro. As such it bears more on the differential effects of ETS versus mainstream smoke that may be important in various disease outcomes, not just CHD. In this study, fibroblasts were exposed for four hours to media containing sidestream smoke at nicotine concentrations (~2 µg/ml) adjusted to reflect typical tissue nicotine levels in nonsmokers following 78 minutes of exposure to ETS in a smoky room, or to a similar preparation of mainstream smoke. Cells were examined microscopically following staining with DIOC6, a stain used to label the endoplasmic reticulum (ER). In control cells not exposed, the ER was well developed, and concentrated around the nucleus but spread throughout the cytosol. By comparison, the ER in cells in sidestream smoke-containing media showed punctate staining reflecting the fragmentation and coalescence of the ER around the

nucleus, whereas the ER in cells exposed to the mainstream smoke solution looked more like that of the control cells. Similarly, sidestream smoke had a differential negative effect on the integrity of Golgi vesicles and the distribution of the chemokine cIL-8 compared to control and mainstream smoke-exposed cells. These data suggest that ETS and mainstream smoke have different cellular effects, possibly indicating different mechanisms of action.

8.3. Chapter Summary and Conclusions

The growing body of evidence continues to support the observation in the 1997 Cal/EPA document that chronic ETS exposure is causally associated with an increased risk for cardiovascular disease in the range of 20-50%. Ultimately, cardiovascular disease is the result of multiple, interrelated changes in the cardiovascular system that manifest primarily as atherosclerosis, the main pathogenic process underlying CHD. Endothelial dysfunction contributes to atherosclerosis (Chilton, 2004; Ross, 1999). The ability of ETS to damage the arterial endothelium is seen in the loss of arterial elasticity and decreased endothelial responsiveness to endogenous signals. Among the causes of vascular damage and the resulting endothelial dysfunction are elevated and oxidized LDL, and circulating free radicals, such as are found in the blood after exposure to tobacco smoke. Vascular damage leads to the uptake and further oxidation of LDL by macrophages at the site of injury, and to plaque formation. ,The ability of ETS to promote plaque growth is evident from both human and animal studies. A mechanistic basis for ETS's atherogenic effects is provided by observations of ETS-associated decreases in HDL-C, increases in peroxidized LDL, compromised antioxidant defenses, and mitochondrial damage after ETS exposure. In addition, ETS is associated with platelet activation and elevated fibrinogen levels that in turn are associated with endothelial damage and plaque formation, respectively.

As a result of the loss of endothelial responsiveness associated with ETS exposure, the coronary arteries are not as responsive to increased tissue demands for oxygen by dilating. This problem is further exacerbated in arteries remodeled by atherosclerotic plaques and carrying blood whose oxygen carrying capacity is decreased by the binding of carbon monoxide from ETS. The elevation of fibrinogen levels and the activation of platelets increase the blood's viscosity, further diminishing the delivery of oxygen to tissues. When the transport of oxygen is compromised, transient or permanent ischemic damage to cardiac and peripheral tissues is more

likely. In individuals with vulnerable plaques, these effects may lead to plaque disruption and the formation of thrombi that in turn may precipitate an ischemic event such as MI or stroke. Indeed, there is some evidence that ETS also contributes to stroke, the etiology of which includes atherosclerosis of the carotid and large arteries of the brain, and degeneration of intracerebral arteries. Research in this area suggests that chronic ETS exposure increases the risk of stroke by about 82% (Bonita *et al.*, 1999).

The deleterious effects of ETS on cardiovascular functioning parallel those observed for other forms of air pollution and for active smoking (US DHHS, 2004). In humans, long term exposure to particulate air pollution has been associated with increased mortality due to AMI, coronary atherosclerosis, and other ischemic heart disease (Pope *et al*., 2004). In vitro, experiments with rat aortic rings exposed to solutions of diesel exhaust particulates showed inhibition of relaxation (Ikeda *et al*., 1995) similar to that reported for rabbit aortic rings exposed to second hand smoke (Hutchison *et al.*, 1999). While the similarities in the biological responses to these various forms of air pollution are not surprising, there are likely to be subtle differences in the mechanisms of action.

In attempts to understand the plausible mechanisms of action of ETS in cardiovascular and other disease endpoints, comparisons with active smoking are often made, frequently with the erroneous assumption that ETS is essentially diluted mainstream smoke. There are, however, significant differences in the chemical composition of ETS and mainstream smoke, some of which are germane to CHD, such as higher levels of CO and nicotine in ETS. That cellular responses are different with ETS versus mainstream smoke exposure was supported by Wong *et al.* (2004) above. In addition, as suggested by Law and Wald (2003), the response of ischemic heart disease to smoke exposure appears to be non-linear with a strong response at low smoke levels that tends to plateau at higher levels.

8.3.1. Cardiovascular Disease Deaths Attributable to ETS Exposure.

In California in 1999, an estimated 81.7% of the adult population (or 19,530,547 persons ≥ 18 years of age) were nonsmokers according to the 1999 California Tobacco Survey (Gilpin *et al.*, 2001). Of this group, 12.75% (2,490,145) were exposed to ETS at work and/or at home during the two weeks preceding the survey. In the following calculations, it is assumed that the general

population is exposed at the same rate, and that the effects of exposure to ETS at home and at work are similar.

The 1997 Cal/EPA document suggested that ETS exposure increased the risk of CHD 20-50%. For CHD risk associated with ETS exposure at home, Ciruzzi *et al*. (1998) found an adjusted OR of 1.68 for exposure to one or more relatives. We expect the risk of CHD to fall in the range of 1.2-1.68. During 2000 in California there were 68,533 cardiac deaths (CDHS, 2000). As stated above, the data suggest that the risk (OR) for cardiovascular disease associated with ETS is in the range of 1.2-1.68. The population attributable risk (PAR) may be calculated from the formula: PAR = p(OR-1)/p(OR-1)+1, where p is the portion of the nonsmoking population exposed to ETS. For nonsmoking indoor workers, the lower OR of 1.2 gives an attributable risk of 0.025 [0.1275*(1.2-1)]/[0.1275*(1.2-1)+1 = 0.025], and the upper OR of 1.68 gives 0.080 [0.1275*(1.68-1)]/ [0.1275*(1.68-1)+1 = 0.080]. Thus the PAR is in the range of 2.5-8.0%. For cardiac death in California in 2000, this translates into 1,700 – 5,483 excess deaths attributable to ETS exposure. For the U.S., there were 515,204 cases of death due to ischemic heart disease in 2000 (Anderson and Arias, 2003). According to Pirkle *et al*. (1996), the rate of ETS exposure among non-smoking adults in NHANES-III was approximately 23%. For the lower end of the range, a = 0.23(1.2-1)/(0.23(1.2-1)+1) = 0.044, and 515,204 x 0.044 = 22,669. For the high end, a = 0.23(1.68-1)/(0.23(1.68-1)+1) = 0.135, and 0.135 x 515,204 = 69,553. Thus the range of excess deaths from heart disease attributable in the U.S. in 2000 was 22,669 – 69,553.

These estimates may be high as they are based on any ETS exposure and exposure intensities were not determined. On the other hand they exclude other ETS exposures outside of work or home, such as in vehicles and in other environments, and they exclude outdoor workers. Thus the actual number of exposed persons and ETS exposure levels may be higher. The upper risk estimate used in this calculation of the PAR is higher than that used in the 1997 Cal/EPA document, reflecting the growing body of evidence more strongly linking ETS exposure to CHD. As a result, the general decline in ETS exposure, reflected in the lower end of this estimate, is partially offset by the stronger causal association.

Thus recent research continues to indicate that ETS exposure increases the risk of cardiovascular disease and stroke. It is also evident that these effects exacerbate or are exacerbated by

underlying conditions, and individuals with other chronic conditions such as diabetes, vascular disease or hypertension comprise a susceptible population at even greater risk from ETS exposure.

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